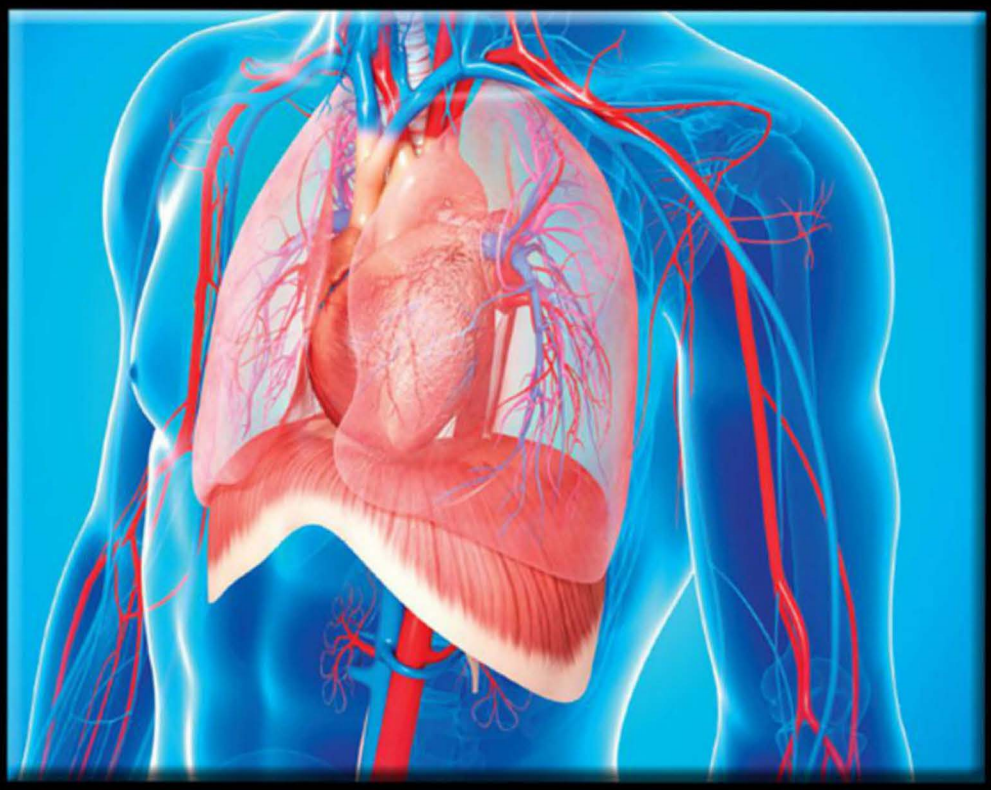
DAVID D. YUH • LUCA A. VRICELLA
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JOHNS HOPKINS
MEDICINE

# TEXTBOOK OF CARDIOTHORACIC SURGERY

SECOND EDITION

Mc Graw Hill Education

# Johns Hopkins Textbook of Cardiothoracic Surgery

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# Johns Hopkins Textbook of Cardiothoracic Surgery

## *Second Edition*

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*To my wife, Dr. Bonnie Hiatt, for accepting my many flaws and idiosyncrasies and for giving me my most cherished gifts, Natalie and Christopher. You each make my life worth living.*

—David D. Yuh, MD, FACC, FACS

*To my wife Simona, for the endless sacrifice of living twenty years with a surgeon … and for brightening every day of my life with her presence, love and partnership.*

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*To my mentors, students, residents, and colleagues—from whom I've learned so much. And for the real teachers in life—my parents Muriel and Harry Yang, my wife Marivic, and children Kristin, Andy, and Alex.*

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—John R. Doty, MD

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# FOREWORD



Paradoxically, our information age has flooded us with an unprecedented volume of medical information (the proverbial "drinking from a firehose"), yet clarity and wisdom still seem as rare as a desert oasis. This long-awaited second edition of the *Johns Hopkins Textbook of Cardiothoracic Surgery* is an arrival welcomed by all surgeons in our specialty, from the novice to the seasoned, who are thirsty for the insight and perspective vested in each chapter. The subtle title change from "manual" to "textbook" belies the substantial additions and enhancements that mark the second edition, including new chapters and authors, key concepts, color accenting, and expanded bibliographies. This work takes its place as one of the most comprehensive yet readable books on the subject and is the best example I know to support the argument that the printed textbook is alive and well, and in great demand.

Although born at Hopkins under Dr Yuh's leadership while he was on our faculty, the project has grown to include experts from many institutions, which parallels the collaborative and information-sharing spirit of our profession. This is particularly so with cardiothoracic surgeons, who delight over sketches of operations drawn on dinnertime napkins and who earn deep satisfaction from warning each other about pitfalls and unseen hazards of procedures and practice. David Yuh and his co-editors Luca Vricella, Steve Yang, and John Doty deserve rich praise for shepherding this effort to collect so much wisdom within a single cover.

Finally, although it may seem odd that a Hopkins book is edited by a Yale surgeon, straddling of these two great institutions by prominent physician educators has precedence in Halsted, Welch, Cushing, Gott, and Reitz, to name just a few. Indeed, three of the four cardiac chiefs at Hopkins since Blalock were Yale graduates. Johns Hopkins and Yale have many similar attributes, not the least of which is a deep tradition and commitment to medical education and the training of young physicians. We are remembered best by the lives we touch, those of our patients and our students.

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*Cardiac Surgeon-in-Charge*
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# PREFACE

Much has changed since first edition of the *Johns Hopkins Manual of Cardiothoracic Surgery* was published in 2007. First, the tried and true Halstedian-based paradigm of cardiothoracic surgical residency training as an 8- to 10-year apprenticeship has been challenged by new duty hour restrictions, intense scrutiny of clinical outcomes, and a seemingly endless parade of evidence-based quality measures and documentation requirements. Whether one deems these changes as progress or not, it is clear that they have affected the environment in which today's residents must learn the craft of cardiothoracic surgery, placing a premium on the time during which they can develop and reinforce their knowledge base from real-life clinical scenarios. Second, the advent of new integrated cardiothoracic surgical residency programs, taking trainees right out of medical school, have made integrated, practical, and concise references with content readily accessible to uninitiated medical graduates even more valuable. Finally, tremendous advances in new technologies, including catheter-based valve delivery systems, less-invasive surgical techniques, new mechanical circulatory devices, and hybrid approaches in the treatment of cardiothoracic disease have added to the already considerable knowledge base that cardiothoracic trainees must assimilate.

We have been gratified that the first edition of the *Johns Hopkins Manual of Cardiothoracic Surgery* occupies a place among highly respected textbooks in our field and, in fact, serves as a sourcebook for the Thoracic Surgical Directors Association web-based curriculum. The second edition of this textbook, renamed the *Johns Hopkins Textbook of Cardiothoracic Surgery*, remains a comprehensive single-volume textbook covering topics in adult cardiac, congenital cardiac, and general thoracic surgery. It is intended as a core reference for all caregivers in the field of cardiothoracic surgery. We again formatted the book to facilitate review, prefacing most chapters with a "Key Concepts" section highlighting the epidemiology, pathophysiology, clinical features, diagnostic and treatment strategies, and outcomes for each topic. Additionally, based on our own critique of the first edition and thoughtful suggestions from its readers, we have made substantial improvements in the new edition, including colorized figures throughout the book, board-review questions and answers, and a greater emphasis on decision-making flow charts that are particularly useful in preparing for oral board examinations.

The content of this textbook reflects the rapidly changing field of cardiothoracic surgery. In addition to the basic curriculum required for certification, we endeavored to include advanced concepts, controversial issues, and new technologies. For example, we have included completely reworked chapters covering Primary Lung Tumors, Mitral Valve Repair, and Mechanical Circulatory Support, as well as entirely new chapters covering Surgical Therapies for Atrial Fibrillation, Cardiac Surgery in Adults with Congenital Heart Disease, and Stem Cell Therapies for Cardiovascular Disease.

As its title implies, most of the contributors to the *Johns Hopkins Textbook of Cardiothoracic Surgery* consist of current or past faculty, residents, fellows, and students at The Johns Hopkins Hospital. The fact that, in the course of our daily routines, we sometimes forget that many of our colleagues are nationally and internationally recognized experts in their respective fields owes to their humility and collegiality. Nevertheless, striving to produce the most authoritative textbook possible, we solicited many experts outside of the Hopkins community. We remain indebted to all of our contributors who generously donated their time and effort to make this a truly collaborative project.

In addition to the contributing authors, we owe thanks to many other individuals. We greatly appreciate the patience and support of our editors and production staff at McGraw-Hill, in particular Christie Naglieri, Brian Belval, and Armen Ovsepyan, as well as the staff at Electronic Publishing Services. We are equally indebted to Kimberly Behrens in the Division of Cardiac Surgery at Hopkins, who took on the onerous and painstaking task of coordinating the many components of this book along with reminding contributors and, yes, Editors to keep on schedule. Also within the Division, Donna Riley, Diane Alejo, Lori Garrison, and Genie Sessa provided invaluable support and friendship. Finally, we wish to express our profound respect and admiration for our colleagues and staff on the cardiac and general thoracic surgical services at The Johns Hopkins Hospital who, in addition to being the very best in their professions, are among the most giving and thoughtful individuals that one could hope to work with.

The sheer magnitude of work involved with assembling the first edition gave us pause in considering embarking on a second edition. We hope that you, like us, are glad that we did. Finally, we all would like to express our profound love and appreciation to our families who, rather than question our sanity, continued to support and encourage us in this undertaking.

*David D. Yuh, MD, FACC, FACS*
*Luca A. Vricella, MD, FACS*
*Stephen C. Yang, MD*
*John R. Doty, MD*

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I

# GENERAL THORACIC SURGERY

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# 1

# Preoperative Evaluation of the Thoracic Surgical Patient

*Kelly K. Nagasawa*
*John R. Doty*

**KEY CONCEPTS**

- Role of preoperative evaluation
  - The role of the preoperative evaluation is to (1) determine the risk and morbidity associated with the proposed operation and (2) identify any patient conditions or factors that can be treated to mitigate the risk of morbidity and mortality.
- History and physical examination
  - The examination should focus on pulmonary and cardiac conditions, as these represent the most common complications after thoracic surgery.
- Functional and performance status
  - The patient's ability to withstand and recover from a major thoracic operation should be assessed prior to surgery. Standard tests such as the Karnofsky score, Zubrod score, DASI questionnaire, stair climbing, and shuttle walk are all useful metrics.
- Pulmonary and cardiac testing
  - Pulmonary function testing remains the cornerstone of preoperative evaluation. $FEV_1$, DLCO, and postoperative predicted values are important predictors of outcomes. Assessment of cardiovascular risk should include noninvasive testing in patients with a history of cardiac disease and more invasive testing as indicated.
- Risk stratification models
  - Mathematical models using the Epithor and Society of Thoracic Surgeons General Thoracic Database can provide reasonably accurate risk stratification for patients undergoing major thoracic surgery.

## INTRODUCTION

Preoperative evaluation of the prospective thoracic surgical patient is a complex process, as patients presenting for major noncardiac thoracic surgery today tend to be older, have underlying chronic obstructive lung disease, and often have multiple comorbidities. Pulmonary and cardiovascular complications occur frequently in the postoperative period and should be aggressively identified and mitigated where possible. The ability to predict and stratify which patients are at a higher risk of complications allows appropriate patient selection and helps guide operative approaches. Preoperative evaluation, therefore, serves two purposes: (a) determining the risk and morbidity associated with the proposed surgical procedure and (b) identifying any patient conditions or factors that could be addressed in the preoperative period to decrease the risk of morbidity and mortality.[1]

## HISTORY AND PHYSICAL EXAMINATION

There is no substitute for a thorough history and physical examination combined with the sound clinical judgment of an experienced physician. There are several specific components in the history of a potential thoracic surgical patient that should be investigated. These important components include presenting symptoms, previous diagnosis of cardiopulmonary disease, comorbid conditions such as diabetes mellitus, renal and liver dysfunction, current medications and allergies, tobacco use, and alcohol use.[1] As the most frequent complications are pulmonary and cardiovascular, the history should focus on these areas.

The physical examination should likewise focus on several signs that indicate important comorbidities. Examination begins with an assessment of overall appearance, looking

especially for evidence of cachexia and generalized wasting. Cervical and supraclavicular lymphadenopathy can indicate metastatic disease. Cardiovascular examination should note murmurs (valvular disease), arrhythmias (atrial fibrillation), and presence of peripheral edema (congestive heart failure). Pulmonary examination should note respiratory rate, use of accessory respiratory muscles, and presence of wheezing or rales. Abdominal examination can confirm the presence of regional tenderness, organomegaly, masses, or adenopathy. The extremities should be examined for equality of pulses, cyanosis, or clubbing. Neurologic examination should focus on motor strength and gait, both of which are important because deficits can affect postoperative mobilization and rehabilitation.

## ASSESSMENT OF PERFORMANCE AND FUNCTIONAL STATUS

Following the history and physical examination, it is critical to estimate the patient's performance and functional status. Performance status assesses the patient's ability to partake in activities of everyday life. The two most common methods are the Karnofsky score[2] and Zubrod (Eastern Cooperative Oncology Group [ECOG]) system.[3] Patients with a Karnofsky score of 80 to 100 percent or an ECOG score of 0 to 1 have essentially normal risk of morbidity and mortality. As the performance status declines, the operative risk increases.

The functional status assesses the patient's current ability to perform physical activity. This can be done with a physical test of locomotion (e.g., 6-min walk or stair climbing), cardiopulmonary exercise testing (CPEx), or self-administered questionnaires such as the Duke Activity Status Index (DASI).[4] A healthy adult should be able to walk at least 1600 ft in 6 min and climb at least five flights of stairs. An alternative to stair climbing is the shuttle walk. Patients who are unable to perform at least 25 shuttles are considered a prohibitive operative risk because this equates to a maximal oxygen uptake of less than 10 mL/kg/min.[5] Oxygen desaturation during testing is considered significant when the $Spo_2$ drops by 4 percent or more with activity.[6,7]

## LABORATORY STUDIES

Standard blood work should include a complete blood count, electrolyte panel, and clotting parameters. Liver function tests and serum calcium levels should be checked in patients with suspected or confirmed malignancy.

## PULMONARY FUNCTION TESTING

Pulmonary function testing is the cornerstone of risk assessment for patients undergoing pulmonary resection. Unfortunately, no single pulmonary function test can perfectly predict the likelihood of postoperative morbidity or mortality. Slinger and Darling[8] have therefore proposed a simple "3-legged stool" of prethoracotomy respiratory assessment that provides a more robust foundation for preoperative respiratory assessment. This algorithm evaluates pulmonary function in three areas: respiratory mechanics (forced expiratory volume in 1 s [$FEV_1$]), parenchymal function (diffusing capacity for carbon monoxide [DLCO]), and cardiopulmonary interaction ($Vo_2max$).

In 2007, the American College of Chest Physicians stated that a patient may proceed directly to surgical resection with no further pulmonary testing if the preoperative $FEV_1$ is greater than 2 L for pneumonectomy candidates and greater than 1.5 L for lobectomy candidates.[9] In addition to providing an estimate of operative risk, preoperative values of $FEV_1$ and DLCO can be used to calculate predicted postoperative values for both $FEV_1$ (ppo-$FEV_1$) and DLCO (ppo-DLCO), which are themselves predictors of operative risk. The ppo-$FEV_1$ can be calculated using the equation of ppo-$FEV_1$ = $FEV_1 \times (1 - [\text{segments resected}/19]/100)$.[10] The ppo-DLCO is calculated using a similar equation.[11] Patients with postoperative $FEV_1$ or a postoperative DLCO greater than 40 percent are generally considered low-risk surgical patients. Although no single test can unilaterally predict the likelihood of major postoperative morbidity, ppo-DLCO has been shown to be a strong predictor of postoperative morbidity and mortality following pulmonary resection.[12]

CPEx is recommended when the ppo-$FEV_1$ or ppo-DLCO is less than 40 percent, or if the product of ppo-FEV1 × ppo-DLCO is less than 1650. The most commonly used result of CPEx is the $MVo_2$, which is the most specific predictor of postoperative pulmonary complications following pulmonary resection.[13] Patients with an $MVo_2$ greater than 15 to 20 mL/kg/min are at low or "acceptable" risk for postoperative morbidity or mortality. Conversely, a patient is considered high risk for surgery if the $MVo_2$ is less than 10 to 12 mL/kg/min.[14]

It is imperative that any patient being considered for major noncardiac thoracic surgery also undergo assessment of cardiovascular risk, as cardiac complications are the second most common cause of morbidity and mortality in the thoracic surgical patients. In general, patients who are on any cardiac medication have a history of a cardiac condition (prior myocardial infarction, congestive heart failure, diabetes, and cerebrovascular disease), or are unable to climb more than two flights of stairs should be referred for cardiology evaluation. The American Heart Association recommends noninvasive testing as a minimum for such patients, with additional invasive testing and intervention as indicated.

## RISK STRATIFICATION

The information and data gathered through history and physical examination, laboratory testing, and pulmonary function testing guide a more educated assessment of the

patient's risk of morbidity and mortality associated with a specific major thoracic surgical procedure. The surgeon can now perform a risk assessment using one of the several available scoring systems. Although no single system is superior, these risk models help in selecting appropriate patients for surgery and educating the patient on general relative risk.

The largest and most validated global risk scoring system is the Thoracoscore. This model was created using a logistic regression analysis of over 15,000 patients from the Epithor database. The Thoracoscore is calculated using nine patient variables significantly associated with the occurrence of in-hospital deaths. These nine variables included age, gender, American Society of Anesthesiology rating (ASA) score, performance status dyspnea score, priority of surgery, extent of surgery, malignant diagnosis, performance status, and composite comorbidity score. An increasing risk profile in a patient is significantly associated with a higher risk of death.

Patients at least 65 years old were found to be at three times higher risk of in-hospital death compared with patients under the age of 55. Malignant pathology and pneumonectomy are also associated with over three times higher risk of mortality. Increasing number of associated comorbidities was also found to increase mortality. There were also 10 major comorbidities that accounted for 95 percent of the documented associated morbidities. These comorbidities can be loosely grouped into pulmonary (smoking, chronic obstructive pulmonary disease [COPD]), cardiovascular (arterial hypertension, heart disease, diabetes mellitus, peripheral vascular disease, and obesity), and chronic impairment (history of cancer, alcoholism).[15]

Kozower and colleagues examined the Society of Thoracic Surgeons General Thoracic Database (STS-GTDB) to create three different models of perioperative risk of lung cancer resection: mortality, morbidity, and combined mortality and morbidity. Data from 18,000 lung cancer resections were used to identify 12 risk factors for mortality following lung cancer resection. These 12 factors were pneumonectomy, bilobectomy, ASA rating, Zubrod performance status, renal dysfunction, induction chemoradiation therapy, steroids, age, urgent procedures, male gender, $FEV_1$, and body mass index.[16] Of these factors, poor performance status (high Zubrod score, poor physical status [high ASA rating]), and induction chemoradiation had the largest impact on morbidity and mortality.

Wright and colleagues also used the STS-GTDB to examine prolonged length of hospital stay (PLOS) as a surrogate of complications following lobectomy for lung cancer. Data from nearly 5000 patients were used to identify risk factors for PLOS. The risk factors associated with PLOS have considerable overlap with the Kozower models and include age, Zubrod score, male gender, ASA score, insulin-dependent diabetes mellitus, renal dysfunction, induction therapy, and percentage predicted $FEV_1$.[17] Table 1-1 summarizes these three risk stratification systems with their various risk factors.

**TABLE 1-1: Summary of Risk Factors for Noncardiac Thoracic Surgery**

| Model | Thoracoscore (Falcoz) | Kozower | Wright |
|---|---|---|---|
| Database | Epithor | STS | STS |
| Risk factors | Age<br>Dyspnea score<br>Male gender<br>ASA rating<br>Priority of surgery<br>Extent of surgery<br>Malignant diagnosis<br>Composite comorbidity score<br>Performance status | Age<br>Zubrod score<br>Male gender<br>ASA rating<br>Renal dysfunction<br>Induction therapy<br>$FEV_1$<br>Steroids<br>Body mass index<br>Pneumonectomy<br>Bilobectomy<br>Urgent procedure | Age<br>Zubrod score<br>Male gender<br>ASA rating<br>Renal dysfunction<br>Induction therapy<br>% predicted $FEV_1$<br>Diabetes mellitus |

## CONCLUSION

The preoperative evaluation of the thoracic surgical patient is a complex process. Although each patient is different, the evaluation process should progress in the same systematic fashion each time. The process always starts with a thorough history and physical examination, followed by laboratory studies and pulmonary function testing. The preoperative assessment ultimately provides the information of each patient's risk of morbidity and mortality and aids both the surgeon and patient in operative decision making.

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## PREOPERATIVE EVALUATION OF THE THORACIC SURGICAL PATIENT BOARD REVIEW QUESTIONS (CHAPTER 1)

1. Which of the following is correct regarding assessment of preoperative performance and functional status?
   A. A Karnofsky score of 10 percent is associated with a low risk of death.
   B. A Zubrod score of 10 is considered normal risk.
   C. A healthy adult should be able to climb one flight of stairs.
   D. Less than 25 shuttles is considered a prohibitive operative risk.
   E. A drop in oxygen saturation of 2 percent during activity is significant.

2. Which is true regarding pulmonary function testing?
   A. If the preoperative $FEV_1$ is greater than 1 L in a lobectomy candidate, no further testing is required.
   B. Predicted postoperative $FEV_1$ greater than 25 percent is a low-risk surgical patient.
   C. Predicted postoperative DLCO greater than 20 percent is a low-risk surgical patient.
   D. $MVO_2$ is the most specific predictor of postoperative pulmonary complications following pulmonary resection.
   E. Patients with an $MVO_2$ greater than 15 to 20 mL/kg/min are high risk for postoperative morbidity or mortality.

3. Which is correct regarding cardiac assessment of the thoracic surgical patient?
   A. Cardiac complications are an uncommon cause of complications after surgery.
   B. Patients with stable congestive heart failure do not require additional testing.
   C. Cardiac catheterization is the initial screening modality.
   D. Diabetes is not a risk factor for cardiac complications.
   E. A patient that cannot climb more than two flights of stairs should have formal cardiology evaluation.

4. Which of the following is not associated with increased mortality in the Thoracoscore model?
   A. ASA rating
   B. Female gender
   C. Malignant diagnosis
   D. Performance status
   E. Age

5. Which of the following is not associated with increased mortality in the STS-GTDB models?
   A. ASA rating
   B. Age
   C. Liver dysfunction
   D. Zubrod score
   E. Induction therapy

## ANSWERS

1. **Answer: D.** The inability to perform 25 shuttles has been correlated with a maximal oxygen uptake of less than 10 mL/kg/min and signifies prohibitive operative risk. A high Karnofsky score (80–100%) or low Zubrod score (0–1) is associated with low mortality. A healthy adult should be able to climb five flights of stairs. A drop in oxygen saturation of 4 percent or more during activity is considered significant.
2. **Answer: D.** Maximal oxygen uptake ($MVO_2$) is the most specific predictor of postoperative pulmonary complications following pulmonary resection. It is acceptable to proceed directly to surgical resection with no further pulmonary testing if the preoperative $FEV_1$ is greater than 2 L for pneumonectomy candidates and greater than 1.5 L for lobectomy candidates. Patients with predicted postoperative $FEV_1$ or predicted postoperative DLCO greater than 40 percent are generally considered low-risk surgical patients. Patients with an $MVO_2$ greater than 15 to 20 mL/kg/min are at low or "acceptable" risk for postoperative morbidity or mortality.
3. **Answer: E.** A patient that cannot climb more than two flights of stairs should have formal cardiology evaluation. Cardiac complications are the second most common cause of morbidity and mortality in the thoracic surgical patient. Patients with a history of a cardiac condition, including congestive heart failure and diabetes, should also be referred for cardiology evaluation. Noninvasive testing is the initial screening modality, with cardiac catheterization reserved for appropriate indications.

4. **Answer: B.** Male, not female gender, is associated with increased mortality. The other risk factors in the Thoracoscore model are age, dyspnea score, ASA rating, priority of surgery, extent of surgery, malignant diagnosis, composite comorbidity score, and performance status.

5. **Answer: C.** Renal, not hepatic, dysfunction is associated with increased mortality. Other risk factors in the STS-GTDB models include age, Zubrod score, ASA rating, induction therapy, and $FEV_1$.

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# 2 Thoracic Trauma

*George J. Koenig Jr.*
*David T. Efron*

## KEY CONCEPTS

- Epidemiology
  - Twenty percent of all trauma patients sustain chest injuries.
- Pathophysiology
  - Thoracic injuries, like with all traumas, can result from blunt or penetrating mechanism. Fractures and soft tissue injuries are common. Compromised breathing remains a particularly urgent concern in these patients, which is unique to thoracic injuries and demonstrates common physiologic signs regardless of cause. Structures that can be injured include the protective bony thorax (ribs, sternum, scapula, and spinal column). The diaphragm inferiorly, and the soft tissue content of the thorax (heart, lungs, esophagus, and great vessels). Severe cardiovascular compromise can also result from injury to the chest.
- Clinical features
  - Outside of the pain of injury, obvious clinical compromise that results from thoracic injury includes primarily signs of respiratory embarrassment and hemodynamic instability. Presenting symptoms vary according to the injured structure. Potential symptoms include dyspnea, tachypnea, and pain on palpation. Signs include contusions, penetrating wounds, subcutaneous emphysema, crepitance, distant or unequal breath sounds on auscultation, muffled heart sounds, tracheal deviation, jugular venous distension, absent upper extremity pulses, shock, and distal neurologic deficit.
- Diagnostics
  - Physical examination including vital signs as part of the primary survey remains the initial most important diagnostic evaluation. Chest x-ray, upright where possible, is desirable. This will delineate injury to most bony structures, identify hemopneumothoraces, raise suspicion about mediastinal injury, and potentially aid in determination of trajectory of penetrating injuries. The patient's hemodynamic status and mechanism of injury guide further diagnostic workup. Focused assessment with sonography for trauma (FAST) ultrasound can identify presence of fluid or the absence thereof in the pericardial sac. Thoracic computed tomography (CT) scan and CT angiography are valuable and reliable in assessing injuries to the great vessels in stable patients at risk and helpful in determining at-risk structures given the trajectory of the penetrating injury. Esophagoscopy, bronchoscopy, and esophagography all play a role in assessing the integrity of these structures and identifying the need for operative repair. In some situations, diagnosis is made necessarily at the time of therapeutic intervention as in the placement of a chest tube for signs of a tension pneumothorax, relief of pericardial tamponade via an emergency department (ED) thoracotomy in an arrested patient, or pericardial window at laparotomy.
- Treatment
  - As with all trauma patients, the best approach in management is delineated by ATLS guidelines. Addressing the need for a secure airway and ensuring adequate breathing and circulation necessitates rapid assessment of the thorax, diagnosis, and intervention for life-threatening abnormalities. Further management depends on structure-specific injuries.
- Outcomes
  - Outcomes for thoracic trauma are widely varied, are injury and mechanism dependent, and vary tremendously according to patient presentation and the specific structures that are injured.

## INTRODUCTION

Approximately 20 percent of all trauma patients sustain injury to their thorax. Thoracic injuries are often obvious on presentation as with penetrating trauma from gunshot wounds or stab wounds. Sequelae may also be easier to identify due to the presence of subcutaneous emphysema or sucking chest wounds. Alternatively, thoracic injury may be indolent in nature as in some cases of blunt trauma where signs of injury may be more subtle, presenting solely with tachypnea or tachycardia. Understanding the mechanism of injury can increase awareness of potential injuries and help direct the diagnostic evaluation. Physical examination is essential in determining injuries as part of your initial assessment.

Guidelines promoted by the Advanced Trauma Life Support (ATLS) course offered by the American College of Surgeons remain the best approach to the care of injured patients. Control of airway, breathing, and circulation is of paramount importance to the successful management of thoracic trauma. After ensuring adequate control of the airway, the entire chest should be exposed. Bilateral chest rise and fall should be observed. The lungs should be auscultated to assess breath sounds. The front, back, and both axillae should be evaluated for external signs of trauma. Other physical findings such as tracheal position, heart sounds, and jugular venous status should be noted. Electrocardiographic leads should be placed and the rhythm determined. A chest x-ray should be obtained. All of this is accomplished as part of the ATLS primary survey.

Several further diagnostic tests are routinely used in the workup of thoracic trauma. The selection of these tests is based on the clinical condition, the mechanism of injury, and the examiner's suspicion of a particular injury. Ultrasound imaging is a simple and rapid method of identifying pericardial fluid and assessing cardiac wall motion,[1] and can be used to detect the presence of a pneumothorax.[2] In hemodynamically stable patients, thoracic computed tomography (CT), aortography, esophagography/esophagoscopy, and transesophageal ultrasound may also have a role in the diagnosis of thoracic injury. Ultimately, thoracotomy may be necessary for both diagnosis and therapy. It is important to note that patients with thoracic trauma frequently demonstrate multisystem trauma. The workup and therapy need to focus on addressing the most life-threatening injuries first, potentially not involving the thorax.

This chapter discusses the diagnosis and management of common thoracic injuries with a focus on the pathophysiologic perturbation that results from trauma. A structure-specific approach is presented (e.g., heart injury, lung injury, etc.), recognizing that injuries to multiple structures often occur simultaneously and need to be concomitantly managed.

## INJURIES TO THE BONY THORAX

The bony thorax comprises the sternum and manubrium anteriorly, a solid rib cage anterolaterally, and the vertebral column posteriorly. The upper thorax is also superficially covered by the scapulae posteriorly, and the clavicles are positioned along the anterior apices bilaterally. These structures combine to confer substantial protection to the underlying soft tissues. The vast majority of information regarding injuries to the bony thorax can be obtained from physical examination and the initial chest x-ray, followed by further radiographic imaging.

## RIB FRACTURES

Injury to the rib cage can range from simple rib fractures to flail segments that can alter breathing mechanics. Simple rib fractures are generally well tolerated. In the absence of underlying pathology, the treatment consists of pain control, incentive spirometry (IS), and aggressive pulmonary toilet. However, multiple rib fractures pose a greater challenge with pain control and can result in major morbidity in the older trauma patient (Fig. 2-1).[3] Morbidities include the need for intubation, development of pneumonia, and prolonged ventilator support. Mortality has been reported to be as high as 22 percent in elderly patients with multiple rib fractures.[4] The risk of death for all ages increases with the number of rib fractures. A large study using the National Trauma Databank showed a significant break point for mortality when more than six ribs were fractured.[5]

In patients with multiple fractures, early epidural analgesia should be considered. High thoracic epidural analgesia has been shown to improve outcomes.[6] The Eastern Association of the Surgery of Trauma Practice management

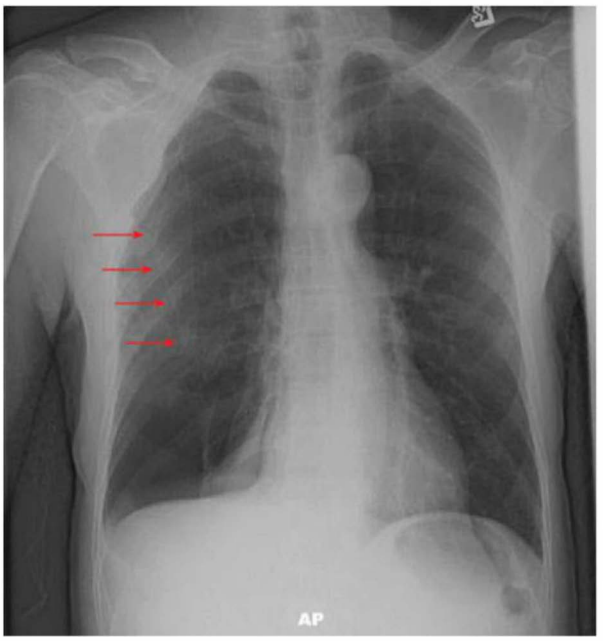



**FIGURE 2-1** Chest x-ray demonstrating multiple right-sided rib fractures (1–9).

guidelines for pain management in blunt thoracic trauma presents Level I recommendations that epidural anesthesia is effective and Level II recommendations that thoracic epidurals should be placed for patients >65 years with four or more rib fractures (when not contraindicated, a thoracic epidural should be used) and considered in younger patients with the same injuries.[7]

Vital capacity and IS can be used to determine if adequate pain control has been achieved. Morbidity and mortality improves if IS is ≥15 mL/kg while achieving adequate pain control. Appropriate analgesia allows the patient to better expand the lung. It also prevents significant atelectasis and helps the patient clear secretions, thereby reducing the risk of pneumonia. In addition to epidural and intercostal blocks, nonsteroidal anti-inflammatory drugs and opioid analgesics play an important role in obtaining adequate pain control.[8]

The location of rib fractures is very important in the workup of the multiply injured patient. Fracture of the upper ribs (first, second, and third) suggests that a significant force was transmitted to the thorax and consequently an increased risk of concomitant great vessel injury; fractures should heighten the suspicion for these injuries and guide diagnostic investigation accordingly. In stable patients, the investigation of choice to evaluate possible great vessel injury is a CT angiogram.[9] Alternatively, fracture of the lower ribs (eighth, ninth, and tenth) should raise the suspicion of injury of solid abdominal organs.

A segment of chest wall that is fractured in multiple places, resulting in an area of the bony thorax that is "free" from rigid fixation, is termed a flail chest. Small flail segments may be tolerated with good analgesia. Posterior flail segments benefit from several natural points of fixation (such as the overlying scapula) and do not contribute to respiratory embarrassment. However, larger flail segments, especially those encountered anteriorly and laterally, may compromise pulmonary function by blunting the negative inspiratory force of spontaneous inspiration. The negative pressure of the descending diaphragm preferentially collapses the chest wall, preventing aeration of the lung. In these cases, the treatment is positive pressure ventilation (PPV) (pneumatic stabilization) until the chest wall mechanics improves. Often, oxygenation is additionally impaired by the underlying pulmonary contusion that nearly always accompanies such an injury. The underlying pulmonary contusion and the protracted recovery usually govern the length of time needed for mechanical ventilation.

Occasionally, the flail segment requires fixation to maintain the integrity of the chest wall to allow ventilation and healing and re-establish lung volume. In addition, some ribs, fractured inward, may pose a threat to intrathoracic structures from sharp edges. A number of commercial systems of plates (both flat and U-shaped) are available for this.

## INJURIES TO THE THORACIC SPINE

Common causes of thoracic spinal fractures include falling from a height, motor vehicle accidents, and penetrating trauma. The entire spinal column is inspected and palpated on secondary survey. Crepitus or tenderness found on examination, suspicion due to mechanism, or the inability to obtain an adequate examination due to other distracting injuries should prompt additional radiographic study. CT scans are the preferred imaging modality for the detection of spinal fractures due to the speed of acquisition and the increased sensitivity and specificity.[10] Because of the mechanisms of injury, many of these patients routinely have CT scans of their chest, abdomen, and pelvis to diagnose injuries within the chest or abdomen. Reconstructions of the thoracic spine can be created from these CT scans, further increasing sensitivity of detection of spine fractures.[11]

These CT reconstructions are helpful in determining if a fracture of the thoracic spine is stable or unstable. Fractures of the vertebral body or transverse process are common whereas unstable fractures are not. There have been several classification systems to describe unstable fractures. The most commonly used classification system was described by Denis et al.[12] This classification system divides the spine into three columns (anterior, posterior, and middle). Disruption of two of the three columns is definitive for an unstable fracture. Unstable fractures require spinal precautions and eventual fixation. Assessment of the spinal canal and injury of the cord often requires magnetic resonance imaging (MRI).

In penetrating trauma, there is no role for the administration of steroids for spinal cord injuries. However, in blunt trauma, the administration of steroids for patients with neurologic deficits is controversial.[13] The basis for their administration was derived from a post hoc analysis of the data collected in the National Acute Spinal Cord Injury Study (NACIS).[14,15] This led to the following recommendations. A bolus of methylprednisolone should be administered within 8 h of injury at a dose of 30 mg/kg/h. If the diagnosis is made within 3 h of injury, the infusion of methylprednisolone should be continued for 23 h at a dose of 5.4 mg/kg/h. If the steroid is started between 3 and 8 h, the infusion should be maintained for 48 h.

However, the results from this post hoc analysis have not been able to be duplicated. In addition, other studies have shown harm from steroid administration.[16] Higher rates of respiratory tract infections, sepsis, urinary tract infections, and wound site infections have been associated with the administration of methylprednisolone. Subsequent evidence-based reviews of the literature have also not shown a benefit.[17-19] The lack of sufficient evidence prompted the deletion of steroid administration for spinal cord injury from the 8th edition of the ATLS course.

## OTHER THORACIC BONY INJURIES

Sternal fractures are most often treated conservatively and do require additional treatment (Fig. 2-2); however, the presence of a sternal fracture can be a strong indicator of severe force injury and should raise awareness for associated injuries, such as blunt aortic, cardiac, and pulmonary injury. Scapular fractures also rarely contribute to the life-threatening nature of chest trauma. Similar to sternal fractures, their presence is a strong indicator of severe force

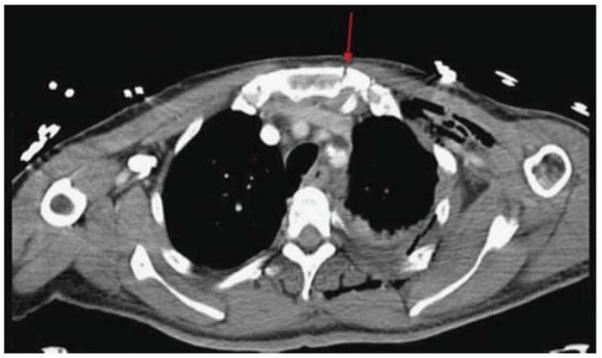


**FIGURE 2-2** Chest CT scan demonstrating a nondisplaced sternal fracture.

injury that should raise suspicion of simultaneous injury to the great vessels. The treatment is typically conservative, focused on pain management.

## LUNG INJURIES

### Pulmonary Contusion

Pulmonary contusion is common after mechanisms of injury that impart substantial kinetic energy to the thorax. In blunt trauma, pulmonary contusion results from the transmission of force across the bony thorax. Due to the elastic nature of immature bone, children may present with a large pulmonary contusion with little evidence of bony thoracic injury. Penetrating injury results in contusion from both the direct tissue lacerations (especially injury to peripheral pulmonary vasculature) and the dissipation of the kinetic energy of the missile.

Alveolar hemorrhage and pulmonary parenchymal destruction typically manifest themselves within hours of injury and usually resolve within approximately 7 days. Clinical symptoms, including respiratory distress with hypoxemia and hypercarbia, worsen for the first 24 to 48 h.[20] The diagnosis of pulmonary contusion is made by the combination of pulmonary dysfunction and radiographic findings (Fig. 2-3A). CT of the chest has been shown to be superior to plain film in identifying a pulmonary contusion (Fig. 2-3B) and may help predict the likelihood of pneumonia, acute respiratory distress syndrome (ARDS), or mechanical ventilation. The main goals of management are pain control, judicious fluid administration, careful hemodynamic monitoring, and aggressive pulmonary toilet. Older patients are particularly susceptible to complications following pulmonary contusion.[21]

### Penetrating Lung Injury

The majority of patients with penetrating lung injury can be managed with tube thoracostomy alone.[22] However, 20 percent of those that require thoracotomy will need some form of lung resection.[23] The extent of the lung resection has been shown to be an independent predictor of hospital mortality. The worst outcomes are seen with pneumonectomy.[24] The higher mortality has encouraged the development of techniques to facilitate rapid and minimal resections. These techniques have used staplers for nonanatomic lobectomy and tractotomy.

Stapled pulmonary tractotomy has been shown in several series to provide rapid and effective exposure to bleeding pulmonary parenchymal vessels and transected bronchi.[25] Unilateral lung isolation is required. This technique can be performed with either single- or double-lumen endotracheal intubations. Most traumas do not allow the luxury of time and stability that is required to place a double-lumen

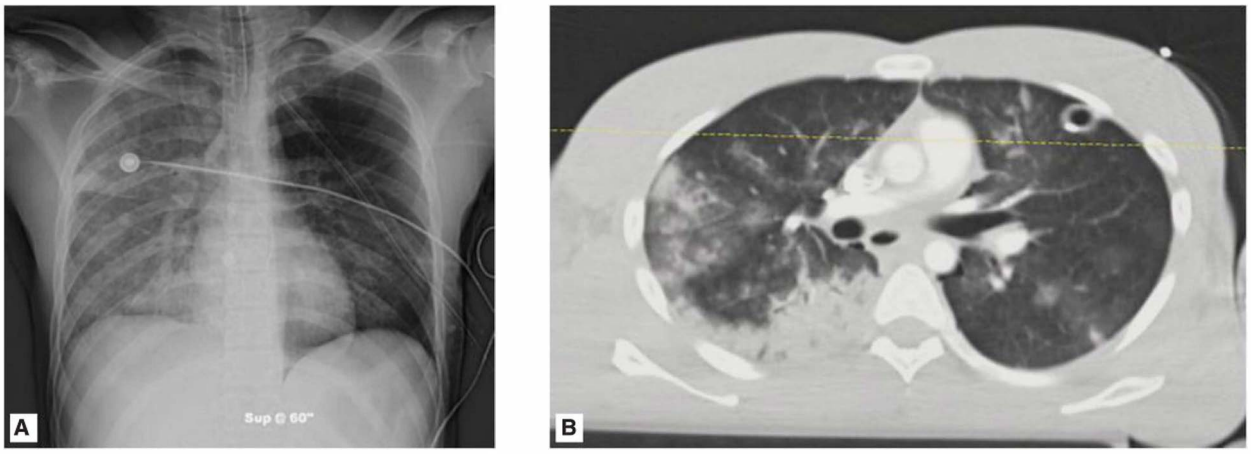



**FIGURE 2-3** **A.** Chest x-ray demonstrating bilateral pulmonary contusions (right > left) following severe blunt trauma from a motor vehicle collision. **B.** Chest CT scan of the same patient (A) demonstrating the pulmonary contusions.

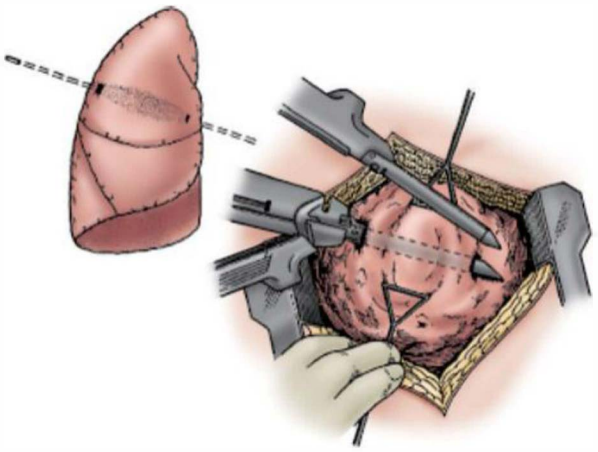


**FIGURE 2-4** Use of GIA stapler to perform tractotomy.

endotracheal tube. If the surgeon is working on the left chest, right mainstem placement of the tube effectively isolates the left lung from ventilation. Conversely, while working on the right chest, a bronchial blocker can be placed in the right bronchus to isolate the right side. These maneuvers may be of benefit if tolerated by the patient because of the reduced positive pressure to the injured lung.

Using a Duval lung clamp placed parallel to the tract of the bullet, the stapling device is positioned so that one of the arms is placed through the entrance and exit wounds of the lungs. When the stapler fires, the bullet tract is exposed fully, allowing the surgeon to directly suture bleeding vessels and transected bronchi (Figs. 2-4 and 2-5). Pulmonary tractotomy for hemorrhage has dramatically decreased the number of patients requiring anatomic resection for trauma.

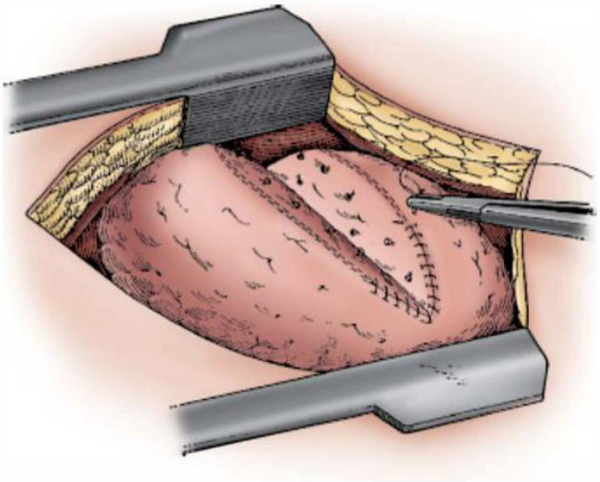


**FIGURE 2-5** Open tractotomy demonstrating access to the deep pulmonary parenchymal vessels and bronchial structures.

An underappreciated and potentially devastating consequence of thoracotomy for ongoing thoracic bleeding is systemic air embolism. The typical trauma patient has depressed intravascular volumes from major ongoing hemorrhage. In addition, the pulmonary architecture is destroyed from the traumatic insult. Both of these circumstances in combination with PPV allow air to escape the small airways and enter the bronchial veins, ultimately leading to a systemic air embolism. While the contributing factors are unavoidable, a heightened sense of urgency and rapid transport to the operating room before intubation is advised. Decreasing the length of time of increased airway pressures prior to controlling ongoing pulmonary bleeding minimizes this risk. Furthermore, when the thorax is entered, occlusion of the pulmonary hilum with a vascular clamp or with the surgeon's fingers can impede the continuous passage of air into the coronary, cerebral, and other systemic arteries.

## Tracheobronchial Injuries

Tracheobronchial injury is uncommon, but immediately life threatening. The true incidence of tracheobronchial injuries is difficult to define since a large portion of these patients will die prior to arrival at a hospital due to the loss of their airway. Based on autopsy reports, it is estimated that 2.5 to 3.2 percent of patients who die as a result of trauma have associated tracheobronchial injuries.[26] More than 80 percent of tracheobronchial injuries are due to blunt trauma located within 2.5 cm of the carina.[27] Tracheobronchial injury can present with subcutaneous emphysema, pneumothorax, massive air leak after tube thoracostomy, or hemoptysis.

In addition to tracheobronchial injury, it is important to recognize the potential for other associated injuries. A delay in the diagnosis of these injuries can potentially affect the overall morbidity and mortality of these patients.[28] Blunt trauma is often associated with multisystem trauma involving not only the chest, but the head, abdomen, and bony structures. Cervical trauma of the airway frequently involve the esophagus, the recurrent laryngeal nerves, the cervical spine and spinal cord, the larynx, and the carotid arteries and jugular veins.[29]

Immediate recognition and stabilization of airway injuries is the first priority in trauma. The diagnosis and management should proceed simultaneously. Patients with respiratory distress and the clinical suspicion of an airway injury should be intubated immediately, preferably with guidance of a flexible bronchoscope. In the unstable patient, you should proceed with direct laryngoscopy and oral intubation with in-line cervical stabilization. Intubation should be followed by diagnostic bronchoscopy. For a bronchial laceration, placement of the endotracheal tube into the uninjured side facilitates repair and improves oxygenation. The operative approach depends on the location of injury. Posterior tracheal injury is repaired via a right posterolateral thoracotomy. The anterior and superior aspects of the upper trachea are best approached via median sternotomy; the distal

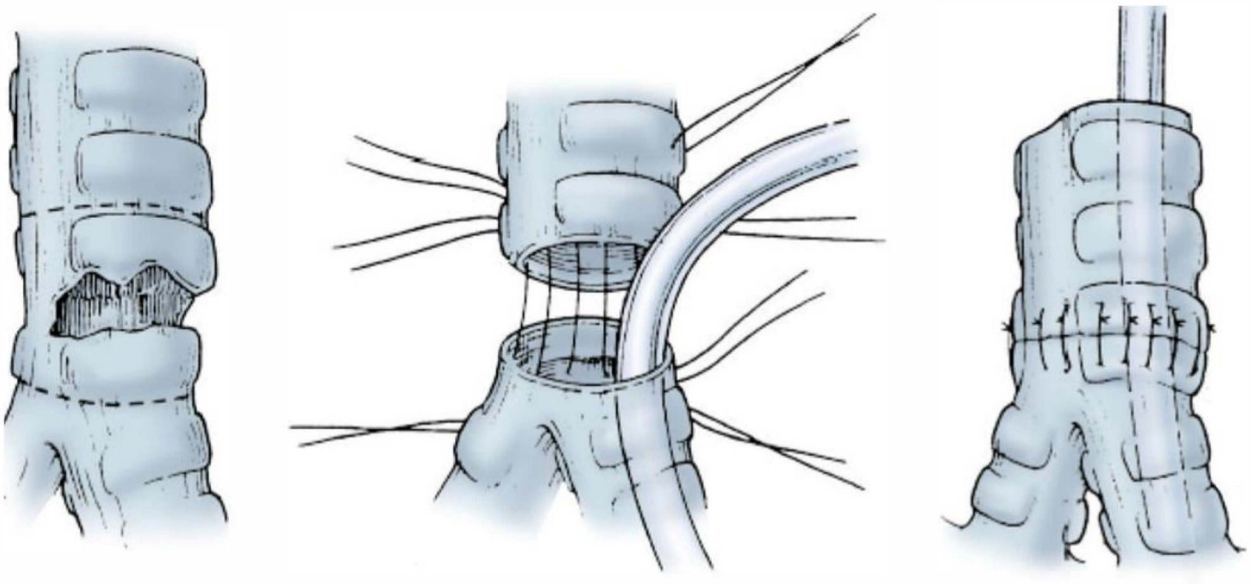


**FIGURE 2-6** Repair of tracheobronchial injuries.

trachea, carina, and left mainstem through the right chest; and the distal left and right bronchi by their respective thoracotomies. Repair is performed with nonabsorbable sutures, with care taken to reapproximate the mucosa (Fig. 2-6).

## CARDIAC INJURIES

### Blunt Cardiac Injury

Blunt cardiac injury (BCI) occurs when an anterior force compresses the chest. The transmitted force and the compression of the heart between the sternum and anterior thoracic spine is the predominant mechanism for BCI. Other mechanisms such as sudden deceleration, where the heart moves freely and strikes the sternum, can also cause BCI. Both of these mechanisms are seen during motor vehicle accidents where an unrestrained driver is propelled forward into the steering wheel. The sudden deceleration of the body and the compression of the chest contuse the heart. Patients sustaining blunt cardiac trauma have been reported to develop cardiac complications, including pump failure, dysrhythmias, myocardial infarction, myocardial rupture, valvular dysfunction, pericarditis, and tamponade.[30]

The true incidence of BCI remains unknown as there is no diagnostic gold standard. Often, the presence of a myocardial contusion is defined by the particular method employed to detect it rather than by the presence of cardiac complications. Electrocardiograms (ECG), cardiac enzymes, and echocardiogram have all been used to identify BCI. However, the lack of a clinical gold standard makes it difficult to consistently define and difficult to interpret the literature. Postmortem, BCI is seen as a well-demarcated hemorrhagic area of the anterior wall of the right ventricle.

Current consensus suggests that patients who present with a mechanism consistent for BCI should have an ECG. The most common dysrhythmia seen with BCI is sinus tachycardia or atrial fibrillation. Other findings include new bundle branch block, ST segment depressions, or ST segment elevations.[31] If an abnormality is present on the ECG, the patient should be admitted for monitoring for 24 to 48 h. Hemodynamically unstable patients should have an echocardiogram performed.[32] There remains controversy regarding cardiac enzymes. At present there are not enough data to recommend using cardiac enzymes for screening of BCI.

### Penetrating Cardiac Injury

Penetrating cardiac trauma remains a highly lethal but potentially salvageable injury.[33] Approximately 90 percent of victims with penetrating cardiac wounds die before reaching the hospital.[34] Patients arriving at the trauma center with vital signs who receive a prompt diagnosis and surgical intervention have substantially better survival rates. Other factors predicting improved survival include stab wounds versus gunshot wounds, single-chamber versus multiple-chamber injury, and the location of thoracotomy (operating room vs. ED (emergency department)).[35,36] Death occurs as a result of cardiac tamponade or exsanguination. The diagnosis of cardiac injury should be entertained in any patients with a precordial penetrating wound. The term "cardiac box" has been used to describe an area of the trunk in which penetrating injuries risk injuring

the heart. It is defined laterally by the midclavicular lines (MCLs), superiorly by the clavicles, and inferiorly by the costal margins.

The diagnosis of tamponade by physical examination can be challenging, since the classic triad of tamponade (hypotension, muffled heart tones, and jugular venous distension) is only present in one-third of patients presenting with the diagnosis and the busy, noisy trauma bay makes physical diagnosis difficult. The presence of penetrating chest trauma in a moribund patient is an indication to proceed with a median sternotomy or left anterolateral thoracotomy. In stable patients, the subxiphoid pericardial view, as part of the focused abdominal sonography for trauma or FAST, can aid in determining the diagnosis of tamponade.[37,38] An equivocal or positive FAST examination necessitates an operative pericardial window. The presence of hemothorax can confound the results of the FAST. The decompression of blood from the pericardial sac into the chest cavity can result in a false negative. In this subset of patients, it may be reasonable to proceed with a pericardial window irrespective of the FAST results. Pericardial windows can be accomplished through either a subxiphoid approach or a transdiaphragmatic approach. The transdiaphragmatic approach is useful if there are concurrent intra-abdominal injuries requiring laparotomy. Regardless of the approach, the chest should be prepped and draped in preparation for a sternotomy.

Pericardial tamponade due to penetrating cardiac injury is the desired lesion that every surgeon looks for when executing the heroic maneuver of ED thoracotomy as it is amenable to repair. Once access is gained to the left chest, a craniocaudad incision is made along the pericardium to deliver the heart and evacuate the hemopericardium while avoiding transection of the phrenic nerve. Potential survivors are the patients who regain cardiac activity and blood pressure. Finger occlusion of the cardiac laceration allows for transport to the operating room for definitive repair.

We prefer to use a 3-0 polypropylene suture on a large (SH or MH) needle to achieve definitive repair. Pledgets facilitate approximation of the laceration and are crucial in the repair of laceration adjacent to coronary vessels. Survivors of cardiac injuries have a small but significant percentage of valvular and septal defects and warrant postoperative echocardiography.[39]

## AORTIC INJURY

The overwhelming majority of patients with aortic injury from penetrating trauma present with exsanguination and impending death. Epidemiologic studies have shown that more than 90 percent of thoracic great vessel injuries are due to penetrating trauma.[40] However, most of these injuries are lethal. Even in the most efficient trauma system or trauma center, there is little hope for salvage.[41]

Alternatively, blunt aortic injury (BAI) is the most common cardiovascular seen in trauma patients.[42] The national incidence of BAI is 0.3 percent of all trauma admissions, and is associated with significant morbidity and mortality.[43] BAI is second to head injury as the leading cause of death after vehicle crashes.[44] The vast majority of these injuries are produced from the deceleration mechanism encountered in motor vehicle accidents. However, they may also occur from falls, pedestrian accidents, and crushing chest wounds.

BAI should be considered in all patients sustaining injuries due to motor vehicle accidents. High-risk occupant characteristics include age ≥60, front-seat occupancy, or unrestrained. High-risk collision characteristics include front- or near-side motor vehicle crash, abrupt deceleration ≥25 mph, crushing of the vehicle >16 in, or intrusion ≥6 in.[45] A chest x-ray should be the initial screening tool. The most common finding prompting further diagnostic workup includes a widened mediastinum, obscure aortic knob, left pleural effusion, first and/or second rib fracture, tracheal deviation, or depressed left bronchus (Fig. 2-7).[46]

There are several theories regarding the pathophysiologic features of BAI. The predominant mechanism of BAI is described as the force of deceleration concentrated at the junction of the fixed and nonfixed segments of the thoracic aorta. Although this is the predominant mechanism, many BAIs are probably caused by a combination of forces, including stretching, shearing, torsion, a "water hammer" (simultaneous occlusion of aorta and a sudden elevation in blood pressure), and the "osseous pinch" effect (entrapment of the aorta between the anterior chest wall and the vertebral column).[47] The isthmus is the most frequent site of rupture (50–70 percent) followed by ascending aorta or arch (18 percent), and the distal thoracic aorta (14 percent).[48,44]

In the last decade, there have been several significant changes in the diagnosis and management of BAI. Among

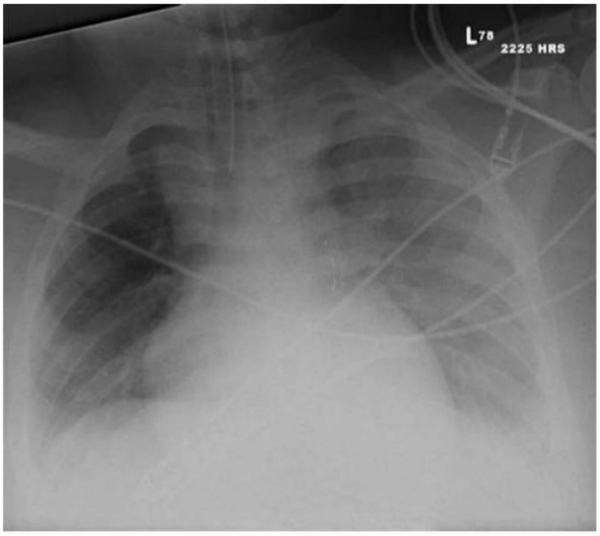



**FIGURE 2-7** Chest x-ray from a patient with a blunt aortic injury following a motor vehicle collision. Note the widened mediastinum, loss of aortic knob, and left pleural capping.

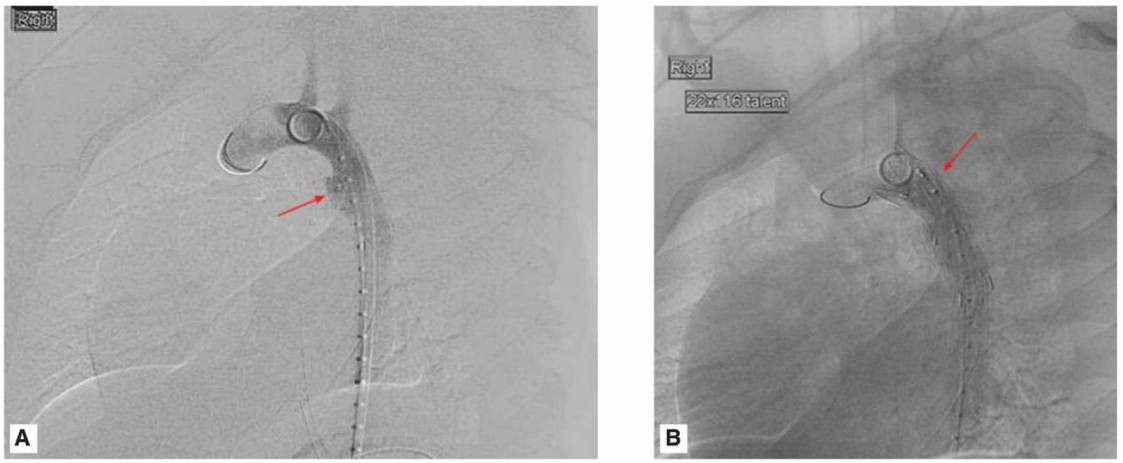



**FIGURE 2-8** **A.** Aortogram demonstrating aortic arch injury from the same patient (Fig. 2-7). Note extravasation of contrast distal to the left subclavian artery. **B.** Aortogram demonstrating endovascular stent in place with exclusion of aortic injury.

them are the liberal use of CT to screen for BAI, replacement of diagnostic angiography by CT, widespread use of β-blockers, planned delayed definitive repair, nonoperative management in selected cases, and introduction of endovascular stent-grafts.

Prompt repair of BAI is preferred when there are no other substantial injuries that would otherwise complicate the repair. However, studies have shown that operative management can be delayed safely to provide time for stabilization of the other injuries.[49] Medical control of blood pressure with β-blockers and nitroprusside is recommended until one is able to proceed with surgery. There are several techniques that have been employed to repair the aorta. While some authors have reported success with the clamp and sew technique, repair with some method of distal perfusion, either bypass or shunt, is preferred to prevent paraplegia. Partial left heart bypass has been shown to be associated with a decreased paraplegia rate in comparison to other techniques.[50]

Endovascular repair, previously used only in high-risk patients, has become the initial procedure of choice in many centers (Fig. 2-8A and B). It has been associated with a significantly lower mortality, but there appears to be a significant number of device-related complications.[51] The long-term results with endovascular repair are not known. The available studies are small and the follow-up is very limited.[52] Furthermore, in older ages, the thoracic aorta can become ectatic and tortuous, and theoretically, there is a risk of device failure. More study need to be completed on the use of endovascular stent grafts, despite their widespread adoption.

## INJURIES TO OTHER GREAT VESSELS

Most of the injuries to the great vessels are the result of penetrating trauma and require immediate intervention. Diagnostic investigation aimed at precise anatomic localization of injury is appropriate only for hemodynamically stable patients. Proximal vessel injuries (pulmonary hilar, innominate, and superior vena caval injuries) are often diagnosed at exploration for massive bleeding. More distal vessels (neck, subclavian, and axillary) may be visualized with duplex ultrasonography, CT angiography, and traditional arteriography. Unequal pulses, asymmetrical artery–artery indices, and expanding hematomas should all raise suspicion for arterial injury. Massive bleeding may be seen with both arterial and venous injury. As with other cases of massive hemorrhage, minimizing time between injury and definitive operative management is key to reducing mortality.

Because of the fixed nature of many vital structures in the mediastinum, suspicion as to which structures are injured is very important to the choice of surgical incision. Timely exposure is crucial for a successful outcome. Injury to the great vessels of the left chest (including left subclavian artery and vein and proximal aorta) typically presents with a massive hemothorax. However, depending on the tract of injury, it can be difficult to accurately predict the bleeding source. Left lateral thoracotomy is the incision of choice for lung parenchymal injuries and access to the descending aorta. A right thoracotomy is the exposure for similar injuries on that side. The subclavian vessels are best approached via an incision directly over the medial third of the clavicle extending from the clavicular head and curving down toward the deltopectoral groove.[53] The clavicle is stripped of its muscular attachments using a periosteal elevator and resected. If the injury is more proximal, this is combined with a median sternotomy. The median sternotomy provides excellent exposure to the most proximal branches of the aortic arch.

If an ED thoracotomy was selected as the initial approach due to massive blood loss, the access is limited to the upper chest. The thoracotomy incision can be extended to a trapdoor type of incision. The incision should be extended from the medial edge along the sternum to the sternal notch and laterally, superior to the left clavicle. The clavicle is then divided within the middle third. With the

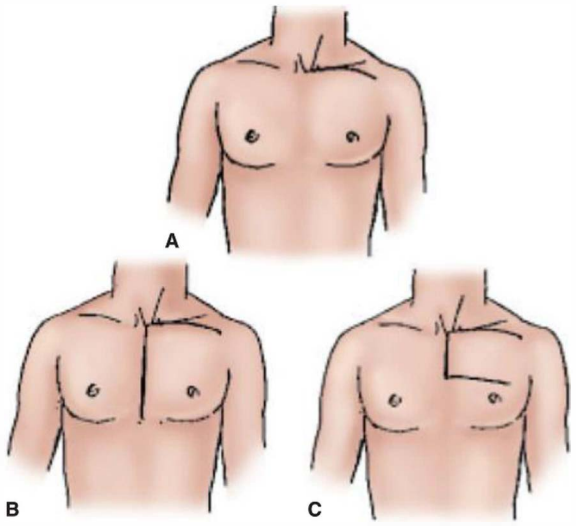



**FIGURE 2-9** Choices of incisions for the approach to injuries of the great vessels. Clavicular incision (**A**), combined clavicular incision and median sternotomy (**B**), and trap door incision (**C**).

segment laterally retracted, access to the distal aortic arch and subclavian vessels is facilitated. However, this incision is highly morbid, carries a significant risk of blood loss due to the extensive muscle division, and requires iatrogenic rib fracture. In addition, the exposure is not significantly better than the exposure achieved with a median sternotomy and clavicular extension. Care must be taken to avoid injury to the brachial plexus and phrenic nerve with this approach (Fig. 2-9).

All subclavian and axillary injuries should undergo repair except in the most severely unstable patients. Temporary shunting may be necessary in these patients. Repair may be achieved by primary anastomosis, autologous vein graft or patch, or interposition of a prosthetic graft. Subclavian vein injuries are repaired only if simple (no significant narrowing of the vessel or need for interposition or patch). Otherwise, ligation of the vein is generally well tolerated. Close monitoring is necessary for possible development of compartment syndrome secondary to limb edema. Prophylactic forelimb fasciotomies are typically not required.

Due to the difficulty and increased morbidity of achieving exposure to repair injuries to the thoracic outlet, recently there has been interest in using endovascular techniques. In unstable patients, the options are limited to immediate exploration. However, these injuries often result in a contained extrapleural hematoma due to the fibrous attachments surrounding the subclavian vessels.[54] In stable patients, a CT arteriogram should be performed to identify the location of the injury and evaluate the mediastinum. Rather than directly exploring the hematoma, an angiogram can be performed and a remote occlusion balloon can be used to obtain proximal control. This results in the conversion of an emergent operation to a semi-urgent operation.[55] Several authors have reported successful exclusion of vessel injuries with covered stentgrafts.[56,57] The initial reports indicate that comparable patency is achieved with less morbidity. Furthermore, the use of endovascular techniques does not preclude subsequent operative intervention or revision that can be performed in a more controlled fashion as an elective procedure.

## Esophageal Injuries

The incidence of esophageal injury after blunt or penetrating trauma is rare. The low incidence is related to several factors. The esophagus is protected by the bony shell of the thoracic cavity and deep location as it spans the entire length of the posterior mediastinum. In addition, esophageal injuries are often associated with other injuries, specifically vascular injuries, which require urgent attention and can lead to death prior to arrival at the hospital or missed diagnosis of small perforations. The treatment of blunt or sharp traumatic injuries to the esophagus is determined by several factors. The timing of the injury, the degree of the injury (contained versus noncontained perforation), and the location of the injury collectively guide subsequent intervention.[58] In penetrating trauma, the most common part of the esophagus injured is the cervical esophagus.

Inpatients who are clinically stable with no hemodynamic instability, the esophagus is best evaluated by esophagography. If the results are equivocal, esophagoscopy should be performed.[59] Clinical findings may include subcutaneous emphysema, mediastinal air, pleural effusion, or unexplained persistent fever for more than 24 h following injury.

As with other structures in the mediastinum, the level of injury dictates the operative approach. For proximal and midthoracic esophageal injury, a right posterolateral thoracotomy is used. Injury of the distal thoracic esophagus is best addressed via a left posterolateral thoracotomy. Esophageal injuries identified early are repaired primarily (in layers, if possible) and often reinforced with tissue-flap coverage (pleural tissue, intercostal muscle, or fundoplication). Those repaired in a delayed manner (>12 h) require wide drainage with multiple tube thoracostomies. Esophageal diversion is considered especially if there is evidence of mediastinitis.

## Diaphragmatic Injuries

Traumatic diaphragmatic injury can occur as a consequence of penetrating or blunt thoracoabdominal trauma. The incidence of diaphragmatic injuries is difficult to estimate because diaphragmatic hernias are often missed by diagnostic imaging and found as incidental findings later in life.[60] For blunt injury, usually seen on the left side, identification of the nasogastric tube in the left hemithorax on chest x-ray suggests herniation of the stomach and is diagnostic of diaphragmatic disruption. In the case of penetrating trauma, the diaphragmatic defect is often too small for herniation in

the acute setting. However, the unrecognized defect, exacerbated by the gradient between the negative intrathoracic pressure and positive intra-abdominal pressure, enlarges over time, resulting in subsequent herniation of intra-abdominal contents into the chest.[61] It is not uncommon for patients to present in the nonacute setting with a diaphragmatic hernia and a previous history of penetrating thoracoabdominal trauma.

Given the potentially dire sequelae of incarcerated bowel contained in a diaphragmatic hernia, operative exploration is recommended to evaluate the diaphragm in the case of left-sided thoracoabdominal trauma. In two prospective studies, patients with penetrating left thoracoabdominal trauma underwent surgical evaluation (laparotomy or thoracotomy for unstable patients, and laparoscopy for stable patients). The incidence of occult diaphragmatic injuries in stable patients was approximately 25 percent.[62,63] Right-sided penetrating diaphragmatic injuries are thought to be of little consequence because right-sided injury is rarely associated with herniation, and the large, fixed liver protects against herniation of intra-abdominal contents.

Both laparoscopy and thoracoscopy are useful techniques for evaluating the diaphragm after penetrating trauma.[64] Thoracoscopy provides excellent visualization of the posterior recesses of the thoracic cavity. This area of the diaphragm is not often seen well with the laparoscopy. Some surgeons advocate this as the preferred approach for posterior wounds from the posterior axillary line to the spine. Thoracoscopy offers several advantages for anterior lower chest wounds. An abdominal procedure can be avoided if the exploration is negative and residual blood and clots can be evacuated from the pleural space. In the absence of a pneumothorax, laparoscopy is the preferred approach. The advantages of laparoscopy are that it avoids an unnecessary thoracostomy tube and abdominal injuries can be assessed. Operative repair of the diaphragm can be performed by either approach if there is no evidence of other intra-abdominal injury.

## SPECIAL CONSIDERATIONS

### Pneumothorax

Pneumothorax is a frequent complication of both blunt and penetrating chest trauma. The entry of air in the pleural space results in partial or total collapse of the lungs, resulting in distant or absent breath sounds. Additional physical findings may include subcutaneous emphysema identified by crepitus over the injured side. Chest x-ray demonstrates opacity and absences of lung markings. The accumulation of air under pressure in the pleural space can lead to a tension pneumothorax. This condition can develop when injured tissue forms a one-way valve, allowing air to enter the pleural space and preventing it from escaping naturally. This is commonly called a "sucking" chest wound or open pneumothorax. To prevent the development of a tension pneumothorax, sterile occlusive gauze should be applied to the chest wall and taped on three sides. This creates a flutter valve that allows air to escape but not enter the pleural cavity. A tension pneumothorax can also result from PPV to an injured lung with an initially small air leak.

The result of a tension pneumothorax is massive overinflation of the affected side, causing a shift of the relatively pliable mediastinal structures toward the opposite side of the chest as well as the flattening of the diaphragm. The increase in thoracic pressure results in a decrease in venous return to the heart and a subsequent decrease in blood pressure. On physical examination, the trachea may appear deviated toward the opposite side.

The clinical picture associated with a tension pneumothorax should prompt immediate decompression without an x-ray in most cases. If a chest tube is not immediately available, a large-bore intravenous catheter can be used to access the chest cavity. The needle should be inserted in the second intercostal space in the MCL. This temporizing maneuver should be followed by the expeditious placement of a thoracostomy tube placed in the fifth intercostal space at the anterior axillary line.

Simple pneumothorax is treated by tube thoracostomy alone. For uncomplicated pneumothorax, moderate-sized (28F) tubes are appropriate. The presentation of an uncomplicated pneumothorax is rare because of associated intrapleural hemorrhage due to trauma. This necessitates the use of a larger tube (36F) to allow for better drainage.

### Hemothorax

Bleeding into the pleural space can occur with virtually any disruption of the tissues of the chest wall and pleura, or the intrathoracic structures (Fig. 2-10). Even minor injury to the chest wall can lead to a significant hemothorax.[65] In addition, intra-abdominal bleeding in patients with diaphragmatic injury can manifest as a hemothorax. The initial treatment of hemothorax is tube thoracostomy. A 36-F chest tube or larger should be placed to ensure effective evacuation of intrapleural blood and re-expansion of the lung. The re-expansion of the lung often tamponades the bleeding and further treatment is not required. However, if the hemothorax is massive or if the bleeding is ongoing, then the patient should be taken to the operating room for prompt thoracotomy and hemostasis. The indications for thoracotomy are discussed later in the Chest Tube Management section.

Following the insertion of a chest tube, a chest x-ray, upright if possible, should be obtained to evaluate placement of the tube and confirm evacuation of the hemothorax (Fig. 2-11). A potential pitfall exists in patients who rapidly accumulate clotted blood in the pleural space. The clotted blood can clog the tube, leading to a false impression that the ongoing bleeding is minimal. The presence of a retained hemothorax and persistent hypotension should raise suspicion that ongoing bleeding is present. Another potential pitfall is kinking of the chest tube resulting in occlusion. The simple maneuver of spinning the chest tube before securing

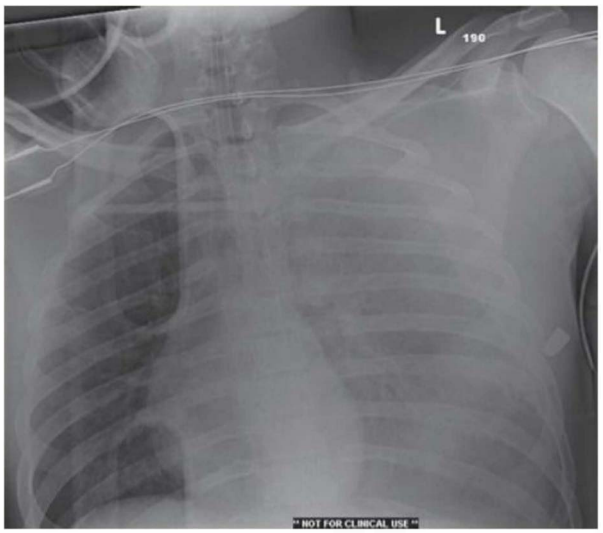



**FIGURE 2-10** Chest x-ray demonstrating massive hemothorax resulting from a gunshot wound.

it in place can eliminate this from occurring. Both of these clinical scenarios can be detected on x-ray, emphasizing the importance of obtaining a postprocedure x-ray.

## Video-Assisted Thoracic Surgery (VATS) for Residual Hemothorax

The majority of traumatic hemothoraces are adequately treated with tube thoracostomy. However, residual posttraumatic hemothorax may occur in 3 to 8 percent of patients.[66]

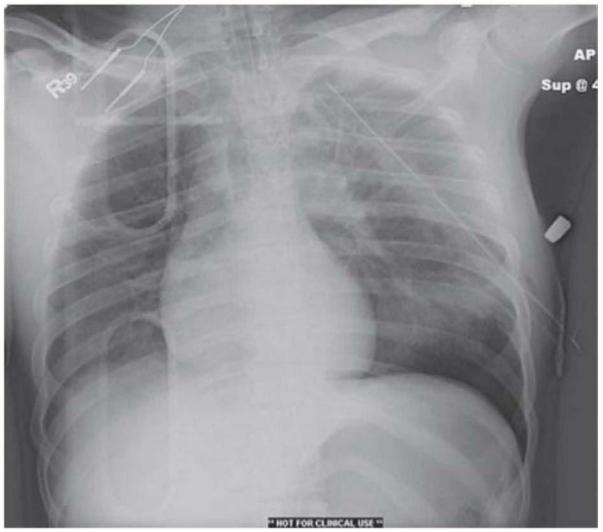



**FIGURE 2-11** Chest x-ray from the same patient (Fig. 2-10) following chest tube placement and resolution of the hemothorax.

The retained blood products are thought to be a major contributing factor in the development of an empyema and subsequent trapped lung.[67]

VATS has a therapeutic role in the evacuation of retained hemothorax. The evacuation of the retained blood products reduces the risk of contamination of the residual blood, development of an empyema, and the chronic changes of a fibrothorax. Subsequently, the need for an open decortication is reduced in these patients and their morbidity decreased. VATS evacuation has been shown to be best accomplished within 5 days after injury when the semisolid clot can be easily suctioned.[68] Patients that are considered for VATS evacuation of persistent hemothorax should be evaluated by CT of the chest, as this has been shown to be superior to chest x-ray in distinguishing free intrapleural blood from contusion, atelectasis, and intraparenchymal hemorrhage.[69]

## Chest Tube Management

Only 10 to 15 percent of all chest wounds require thoracotomy, whereas the remaining 85 percent can be managed with a closed tube thoracostomy.[70] Thoracotomy should be performed for hemodynamically unstable patients with chest trauma that are not responsive to adequate resuscitation. Other indications for thoracotomy are greater than 1500 mL of blood evacuated initially on chest tube insertion, ongoing blood loss (>200–300 mL/h for 4 h), and persistent hemothorax despite adequate drainage with two chest tubes (Table 2-1).

If the patient's condition permits, tube thoracostomy should be performed using sterile technique. A large-bore 36-F chest tube should be inserted in between the fourth and fifth inner costal space. For patients with hemopneumothorax, the chest tube can be removed when the output decreases to <200 mL/24 h and there is no recurrence of pneumothorax on water seal. Thoracoscopy should be considered for residual hemothorax.

A significant complication associated with tube thoracostomy, although rare, is empyema. In trauma patients, the risk is further increased due to the mechanism of the

**TABLE 2-1: Indications for Thoracotomy**

| |
|---|
| **Penetrating injury with cardiac arrest** |
| Immediate output of >1500 $cm^3$ of blood from the chest tube insertion |
| Ongoing blood loss (>200–300 $cm^3$ of blood per hour over 4 h) |
| Persistent hemothorax despite adequate chest tube placement |
| Ongoing massive air leak |
| Evidence of esophageal injury |
| Evidence of diaphragmatic injury |
| Large chest wall defect requiring reconstruction |

trauma. When a bullet or knife penetrates the chest cavity and enters the pleural space, bacterial contamination occurs. The use of antibiotics to prevent the development of empyema has been suggested. Current recommendations based on consensus are that a first-generation cephalosporin should be administered prior to chest tube placement for traumatic hemopneumothorax, and continued for no longer than 24 h. Longer courses of therapy have not been shown to decrease the incidence of septic complications. Interestingly, the data suggest that there may be a reduction in the incidence of pneumonia but not empyema in trauma patients receiving prophylactic antibiotics when the chest tube is placed.[70]

## Emergency Department Thoracotomy

Emergency department resuscitative thoracotomy (EDRT) is an aggressive procedure to save a dying patient. This heroic lifesaving measure is reserved for patients with penetrating injury of the torso who have lost vital signs in transport to, or shortly after arriving at, the hospital. Prognostic factors that have been identified in the literature include mechanism and site of injury, presence of vital signs or signs of life at the scene and in the ED, total field time, and the expertise of the person performing the procedure.[71]

Patients sustaining penetrating trauma have a statistically better chance of survival after EDRT compared with cardiac

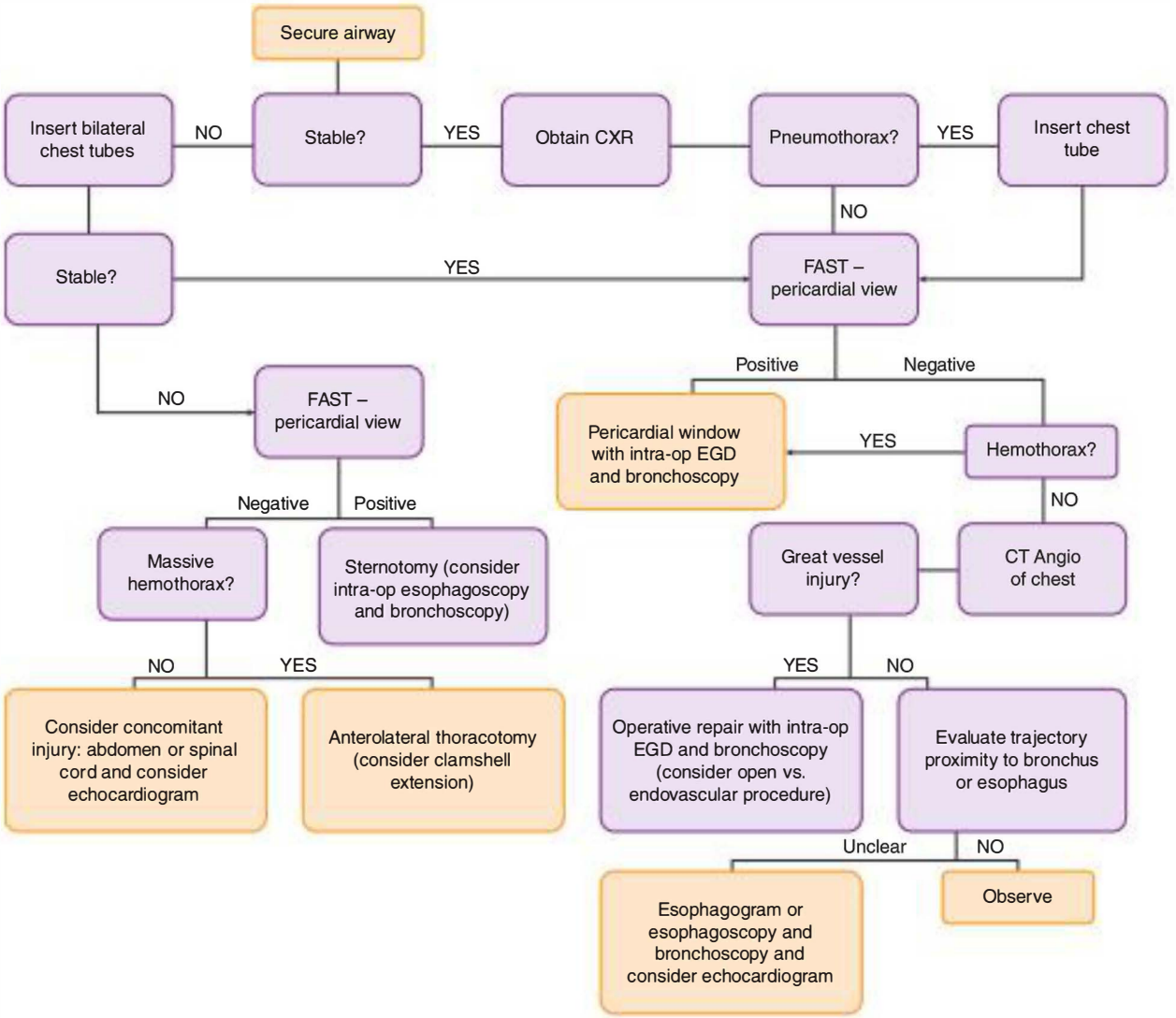



**FIGURE 2-12** Decision tree algorithm for the management of transmediastinal gunshot wounds.

arrest victims from blunt trauma. Greatest survival rates are achieved in the subset of patients with stab wounds to the right ventricle and with pericardial tamponade.[72] Among patients with penetrating trauma, those with stab wounds have a better survival rate than those suffering cardiac arrest from gunshot wounds.[73] Patients sustaining cardiac arrest subsequent to blunt trauma have an extremely poor prognosis (1–2 percent survival).[74]

After determining the need for an ED thoracotomy, the patient's left arm should be placed above the head to provide unimpeded access to the left chest. The thoracotomy incision should start on the right side of the sternum. This saves time if sternal transection is required for additional exposure. The initial incision is carried transversely across the chest, beneath the nipple, and curved slightly toward the patient axilla following the natural curvature of the rib cage. The intercostal muscles are divided sharply with care not to damage the underlying parenchyma. A right chest tube should be placed simultaneously by another member of the trauma team. A Finochietto retractor is placed and the intercostal space is widened for exposure. The pericardium is easily identified medially and inspected. A bulging pericardium is suggestive of pericardial tamponade and requires immediate decompression. The pericardial sac is open longitudinally to avoid injury to the left phrenic nerve. If there is no evidence of tamponade, the thorax is inspected for sites of bleeding and injury.

To optimize blood flow to the carotid and coronary circulation, the thoracic aorta is occluded either by an atraumatic vascular clamp or by direct compression against the vertebral column. Clamping the aorta has the advantage of freeing the surgeon's hands for other procedures such as cardiac massage. However, the esophagus can be easily injured in the process. An orogastric tube can be inserted to aid in the differentiation between the esophagus and the aorta. Direct compression avoids the risks of esophageal injury but necessitates an additional hand in an already limited field.

The initial execution of a clamshell thoracotomy should be performed in hypotensive patients with penetrating wounds to the right chest. This exposure provides immediate, direct access to a right-sided pulmonary or vascular injury while allowing access to the pericardium from the left side for open cardiac massage. When visualization of penetrating wounds in the aortic arch or major branches is needed, the superior sternum is additionally split in the midline. Recovery of hemodynamics allows for prompt travel to the OR for definitive repair.

## Transmediastinal Gunshot Wounds

Hemodynamically unstable patients with transmediastinal gunshot wounds typically receive rapid tube thoracostomy and are transported to the operating room. However, in stable patients, the order of the diagnostic workup has been debated. Historically, the assessment of the aorta preceded the investigation of the esophagus. This notion has been challenged because victims of gunshot wounds of the esophagus are more commonly stable from a hemodynamic standpoint than their counterparts with aortic injuries.[75] However, with the increased speed and resolution of CT, an accurate assessment of potential mediastinal injury can be obtained readily without the delay of an invasive procedure. CT provides a noninvasive means to evaluate missile trajectories and the great vessels.[76] Based on the CT findings, additional testing may be indicated such as esophagoscopy, bronchoscopy, or echocardiography (Fig. 2-12).

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## THORACIC TRAUMA BOARD REVIEW QUESTIONS (CHAPTER 2)

1. A 55-year-old unrestrained driver involved in a high-speed motor vehicle collision sustains multiple right-sided rib fractures. Which statement is correct regarding the management of this patient?
   A. Incentive spirometry is not useful in predicting morbidity and mortality.
   B. A thoracic epidural catheter is contraindicated in the setting of multiple rib fractures.
   C. Tube thoracostomy should be performed prophylactically.
   D. Thoracic epidural analgesia has been shown to improve outcomes.
   E. Elderly patients with multiple rib fractures have lower morbidity and mortality compared with young patients.

2. Which patient should receive resuscitative thoracotomy in the emergency department?
   A. An 18-year-old man with hypotension from a penetrating anterior chest wound
   B. A 35-year-old restrained driver found pulseless at scene with no electrical activity on ECG on arrival to the trauma center
   C. A 23-year-old man with hypotension from penetrating left chest wound after intubation and positive pressure ventilation
   D. A 64-year-old woman with penetrating anterior chest wound who becomes tachycardic and then pulseless
   E. A 16-year-old man with no cardiac activity after 30-ft fall from ladder

3. A 36-year-old woman suffers a gunshot wound that enters the left chest and exits the right chest. She is hemodynamically stable with no respiratory distress. Chest x-ray shows no retained fragments, pleural effusion, or pneumothorax. What is the correct next step in management?
   A. FAST examination
   B. CT scan
   C. Barium swallow
   D. Sternotomy for exploration of the mediastinum
   E. Subxiphoid window

4. A 45-year-old man sustains multiple right-sided rib fractures after a 20-ft fall. A chest tube is inserted for a hemopneumothorax. Which of the following is *not* an indication for thoracotomy?
   A. Drainage of 2000 mL of blood after chest tube insertion.
   B. Persistent hemothorax after placement of a second chest tube.
   C. Ongoing blood loss exceeding 250 mL/h over 4 h.
   D. Hemodynamic instability.
   E. Air leak.

5. An 18-year-old restrained passenger complains of abdominal pain and shortness of breath after a side impact motor vehicle collision. There is opacification of the left chest on initial chest x-ray. What is the correct next step in management?
   A. Tube thoracostomy
   B. Barium swallow
   C. Exploratory laparoscopy
   D. Emergent laparotomy
   E. Insertion of nasogastric tube

## ANSWERS

1. **Answer: D.** Thoracic epidural analgesia has been shown to improve pain control and overall outcomes in older patients with multiple rib fractures. This approach is not contraindicated and may also be useful in younger patients. Incentive spirometry can be useful in predicting morbidity and mortality, which is higher in the elderly population. Tube thoracostomy should not be performed prophylactically.
2. **Answer: D.** ED thoracotomy is reserved for patients that lose vitals or signs of life en route to the trauma center or a have a witnessed arrest. Hypotension can result from hemothorax or pneumothorax, which requires placement of a chest tube rather than thoracotomy. The best outcomes are seen in patients that sustain a penetrating injury; there is debate about whether ED thoracotomy should be offered at all after a blunt injury.
3. **Answer: B.** A hemodynamically stable patient with a transmediastinal penetrating injury should be evaluated with CT, as this is the most rapid method to evaluate for both aortic and esophageal injury. Focused assessment of sonography for trauma (FAST) is useful for

pericardial effusion, which is unlikely in a stable patient. Barium swallow may be necessary, but only after CT scanning. Operative exploration is not indicated in this stable patient.

4. **Answer: E.** An air leak after insertion of a chest tube for multiple rib fractures is common and is not an indication for thoracotomy. Massive initial drainage (>1500 mL), persistent hemothorax, ongoing excessive chest tube output (>250 mL/h over 4 h), and hemodynamic instability despite adequate volume resuscitation are all indications for thoracotomy.
5. **Answer: E.** The patient's findings are concerning for diaphragmatic rupture, and insertion of a nasogastric tube will identify location of the stomach on a follow-up chest x-ray. If the nasogastric tube is above the expected location of the diaphragm, blunt injury of the diaphragm is suspected and additional evaluation initiated.

3

# Pulmonary Physiology, Function Tests, and Bronchoscopic Techniques

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**KEY CONCEPTS**

- Epidemiology
  - Pulmonary complications occur in 5 to 10 percent of all surgical patients and have been shown to prolong hospital stay by 1 to 2 weeks. Approximately 25 percent of deaths within the first week after surgery are due to pulmonary complications.
- Pathophysiology
  - Pneumonia occurs in 10 to 40 percent of patients after major surgery and is associated with a mortality rate of 30 to 45 percent. General anesthesia can decrease lung volumes by 30 to 40 percent, and this decrease may persist for 1 to 2 weeks postoperatively.
- Clinical features
  - Cardiothoracic surgery is associated with the highest frequency of pulmonary complications. Risk factors include the type of surgery, general anesthesia, length of surgery and general anesthesia, smoking, chronic obstructive pulmonary disease, age, obesity, functional status, and a history of dyspnea.
- Diagnostics
  - Preoperative evaluation should include a directed history and physical examination to identify those patients at particular risk for pulmonary complications. Pulmonary function tests with spirometry and arterial blood gases (ABGs) should be obtained for any patient undergoing lung resection. For further risk stratification, cardiopulmonary exercise testing (CPET) is indicated in high-risk patients who do not have adequate predicted postoperative lung function. Alternatives to CPET include the shuttle-walk or stair-climb test.
  - Bronchoscopy is an essential tool in the preoperative work for diagnosis, staging, and surgical planning.
- Treatment
  - Inhaled bronchodilators may successfully reverse some cases of obstructive pulmonary disease.
- Outcomes
  - Preoperative pulmonary function evaluation can stratify patients for risk, thus identifying those who can safely undergo major cardiothoracic surgery and minimizing the risk of significant morbidity and mortality.
  - Appropriate nodal staging is essential in the workup of lung cancer patients and essential for surgical planning.

## INTRODUCTION

Pulmonary complications in the perioperative period remain a significant cause of morbidity and mortality and occur in 5 to 10 percent of all surgical patients. Not only have these complications been shown to prolong hospital stay by an average of 1 to 2 weeks but 25 percent of deaths within the first week after surgery are reportedly due to pulmonary complications.[1-4] One way to minimize these complications is with the appropriate use of preoperative testing. Both noninvasive preoperative testing such as pulmonary function testing and minimally invasive testing such as bronchoscopy can add valuable information to the workup of the preoperative cardiothoracic patient. In this chapter, we will review the burden of postoperative complications, basic pulmonary physiology, the preoperative

pulmonary workup for the cardiothoracic surgical patient, and the role of bronchoscopy for the diagnosis and staging of lung cancer.

## PERIOPERATIVE PULMONARY COMPLICATIONS

In the postoperative period, there are a wide range of pulmonary complications (Table 3-1) that can occur in patients with underlying lung disease. Postoperative pneumonia can occur in 10 to 40 percent of patients and is associated with a mortality rate of 30 to 45 percent after major surgical procedures. The benefits of a thorough preoperative evaluation include the identification of patients with underlying lung disease, modification of risk factors, optimization of medical management, avoidance of elective surgery in high-risk patients, and prevention of inappropriate surgical resection by appropriately staging for lung cancer.

There are multiple risk factors for postoperative pulmonary complications including patient related factors as well as the specific type of surgery and anesthesia. The location and type of surgery being performed are the major determinants of pulmonary complication risk. Cardiothoracic surgery has been repeatedly shown to have the highest frequency of pulmonary complications.[5] Anesthesia is also important in determining postoperative risks as it has been shown that general anesthesia can decrease lung volumes by 10 to 30 percent for which these changes may persist for 1 to 2 weeks postoperatively. The combination of thoracic surgery and general anesthesia often leads to decreased lung volumes, worsening gas exchange, and impairment in airway clearance, all of which may result in severe complications, especially in patients with underlying lung disease.

Patient-specific risk factors that have been identified are listed in Table 3-2. Appropriate identification and modification of reversible risk factors is an important component of the preoperative evaluation and one that can significantly reduce operative risk. One of the most important modifiable risk factors is smoking cessation several weeks prior to elective surgery;[6] cessation 2 weeks prior may in fact increase postoperative complications, likely as a result of the impaired mobilization of secretions.

**TABLE 3-1: Postoperative Pulmonary Complications**

| |
|---|
| Prolonged need for mechanical ventilation |
| Respiratory failure |
| Pneumonia |
| Bronchospasm |
| Acute respiratory distress syndrome (ARDS) |
| Atelectasis |
| Pleural effusion |
| Pneumothorax |

**TABLE 3-2: Patient-Specific Risk Factors for Pulmonary Complications**

| |
|---|
| Tobacco history |
| Chronic obstructive pulmonary disease |
| Restrictive lung disease |
| Age |
| Obesity |
| Functional status |
| Dyspnea |
| Impaired sensorium |

## INDICATIONS FOR PREOPERATIVE PULMONARY FUNCTION TESTING

Identifying patients who are at increased risk of pulmonary complications begins with a detailed history and physical examination. Any unexplained dyspnea at rest or on minimal exertion should warrant a more thorough evaluation prior to any elective surgical procedure. Smoking cessation should be recommended to all patients, ideally having them quit at least 2 weeks before the surgery. If a patient has any history of prior lung disease, significant tobacco use, or dyspnea with mild exertion, they warrant pulmonary function testing before any high-risk elective surgical procedure.

The American College of Physicians recommends preoperative pulmonary function testing for the following patients[7]:

- All patients with a history of tobacco use or dyspnea who are undergoing cardiothoracic or upper abdominal surgery.
- Any patient with unexplained dyspnea or pulmonary symptoms who is undergoing head, neck, orthopedic, or lower abdominal surgery.
- All patients undergoing lung resection.

Preoperative pulmonary function testing most often consists of spirometry, diffusion capacity, and sometimes arterial blood gas (ABG) analysis. Patients undergoing lung resection surgery are clearly at a particularly high risk of pulmonary complications and warrant a more thorough evaluation.

## PREOPERATIVE EVALUATION OF THE LUNG RESECTION CANDIDATE

There are several risk factors that have been identified to increase complications in patients undergoing lung resection. Lung resection surgery is associated with significant morbidity in up to 50 percent of patients and death in up to 8 percent.[8] The type of resection is a major determinant of

operative risk, with pneumonectomy having a greater operative morbidity and mortality than lobectomy.[9]

Both pulmonary function testing with spirometry and an ABG measurement should be obtained on all patients considered for lung resection surgery.[10] Baseline hypercapnia and hypoxia at rest or during exertion predicted an increased surgical morbidity.[11]

Spirometry is the most accurate and predictive pulmonary function test available. It can identify low-risk patients who can proceed directly to surgery as well as higher-risk patients who warrant further investigation. It is recommended that patients have a postoperative forced expiratory volume in 1 s ($FEV_1$) of greater than 0.8 L or 30 percent of predicted and also a postoperative diffusing capacity of carbon monoxide (DLCO) of greater than 40 percent predicted. If the preoperative $FEV_1$ is greater than 2.0 L for a pneumonectomy, or greater than 1.5 L for a lobectomy, no further pulmonary testing is required, and the patient can proceed directly to lung resection. All patients who have an $FEV_1$ below these cutoffs require more extensive evaluation prior to lung resection (Fig. 3-1). These additional tests are used to help predict postoperative pulmonary function. The quantitative perfusion scan is used to estimate the percent of functional lung that is being resected.[12] The estimate of postoperative pulmonary function is calculated with the following equation:

$$\text{Predicted } FEV_1 = \frac{\text{preoperative } FEV_1 \times (100 - \text{percent of lung to be removed})}{100}$$

$$= \frac{\text{preoperative } FEV_1 \times (19 - \text{number of segments to be removed})}{19}$$

The same equation can be used to calculate the predicted postoperative DLCO. Any patient with a predicted postoperative $FEV_1$ and DLCO above the minimum values outlined above should have a standard risk of pulmonary complications. A patient who does not have an adequate predicted postoperative lung function based on the above testing should not be denied surgery without further evaluation if he or she otherwise appears to be an appropriate surgical candidate. These higher-risk patients should undergo cardiopulmonary exercise testing (CPET) for further risk stratification. The measurement of the maximal oxygen consumption, $\dot{V}O_{2max}$, by CPET is the most specific predictor of postoperative pulmonary complications following lung resection surgery.[13] If the measured $\dot{V}O_{2max}$ is greater than 20 mL/kg/min, the risk of postoperative pulmonary complications is low, and the patient may be safely offered surgical resection. Patients with a $\dot{V}O_{2max}$ <15 mL/kg/min have a moderately increased risk of surgery, and a $\dot{V}O_{2max}$ less than 10 mL/kg/min is associated with a high surgical risk.

Since lung resection is the only cure for many patients with localized lung cancer, the strategies of pulmonary function testing have been designed to maximize their sensitivity in identifying all patients who can safely tolerate lung resection; these strategies must be tailored to the goals of the individual patient.

## ARTERIAL BLOOD GAS ANALYSIS

ABG analysis is a readily available test that provides useful information to identify the high-risk surgical patient. The ABG measurement should be performed at rest and breathing ambient air, if possible. The partial pressure of oxygen ($P_{O_2}$) reflects the adequacy of gas transfer from the alveoli to the blood and when, measured at sea level, the normal $P_{O_2}$ ranges from 85 to 100 mm Hg. The $P_{O_2}$ as a measurement of oxygenation should be interpreted in terms of the oxygen dissociation curve (Fig. 3-2). Since a majority of oxygen in the blood is bound to hemoglobin, relative changes in $P_{O_2}$ can reflect a wide range of changes in oxygen carrying capacity depending on the slope of the oxygen dissociation curve. Changes in $P_{O_2}$ on the steep part of the oxygen dissociation curve reflect large changes in blood oxygen content. In contrast, changes in $P_{O_2}$ on the flat part of the oxygen dissociation curve, $P_{O_2}$ greater than 70 mm Hg, lead to only minor differences in oxygen content. The alveolar–arterial oxygen gradient [A–a gradient = $P_iO_2 - (PaCO_2/R) - PaO_2$] is a more sensitive measurement of gas exchange problems. Since pulmonary function normally declines with age, the normal values for A–a gradient depend on the age of the patient and can be calculated based on the following equation.

$$\text{Normal A–a gradient} = 2.5 + \frac{1}{4}\text{age} \pm 2$$

An elevated A–a gradient can be due to ventilation/perfusion mismatching, diffusion defects, or shunt.

The partial pressure of carbon dioxide, $P_{CO_2}$, is a measurement of $CO_2$ production ($\dot{V}CO_2$) and alveolar ventilation ($\dot{V}_A$); that is, $PaCO_2 = \dot{V}CO_2/\dot{V}_A$. Therefore, an increase in $CO_2$ production or a decrease in alveolar ventilation leads to an increase in $P_{CO_2}$. Normally $P_{CO_2}$ is tightly regulated, with normal values at rest between 38 and 42 mm Hg, and is not affected by age. Hypercapnia can be due to a wide range of causes. Alveolar ventilation ($V_A$) is dependent on both minute ventilation ($V_E$) and dead-space ventilation ($V_D$) in the relationship where $V_T$ is the tidal volume:

$$V_A = V_E (1 - V_D/V_T)$$

Conditions such as emphysema or interstitial lung disease lead to an increase in $\dot{V}_D$ and a corresponding decrease in $\dot{V}_A$, which can result in hypercapnia with exertion or at rest. Hypoventilation can be due to a number of causes besides parenchymal lung disease, including musculoskeletal and neurologic causes. ABG analysis provides a simple measure of oxygenation and ventilation and the presence of hypoxia or hypercapnia should identify a higher-risk patient who warrants a more thorough evaluation.

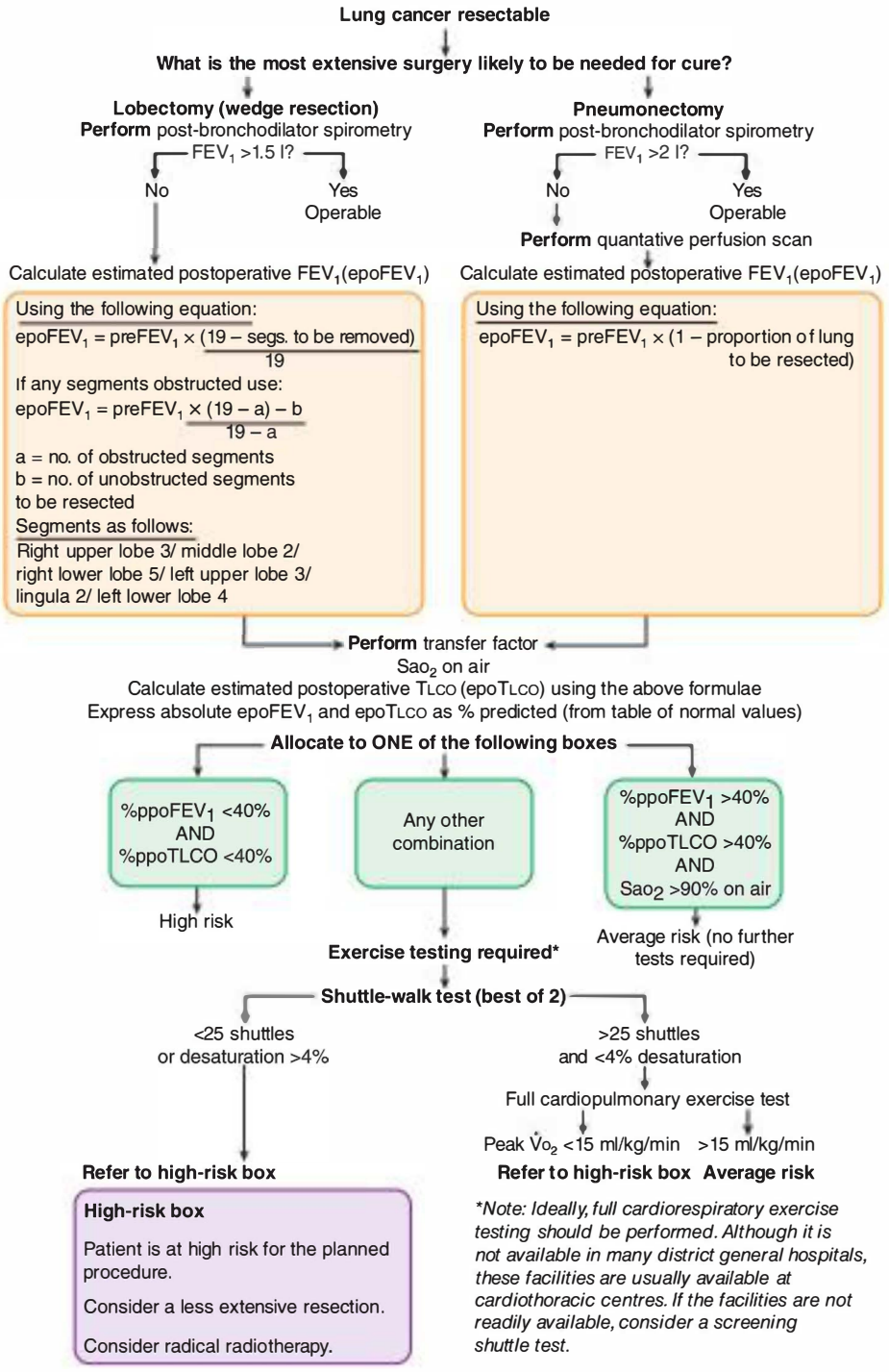



**FIGURE 3-1** Algorithm for preoperative evaluation of candidates for lung resection. (Reproduced from BTS guidelines: guidelines on the selection of patients with lung cancer for surgery. *Thorax* 2001;56(2):89–108. With permission from BMJ Publishing Group, Ltd.)

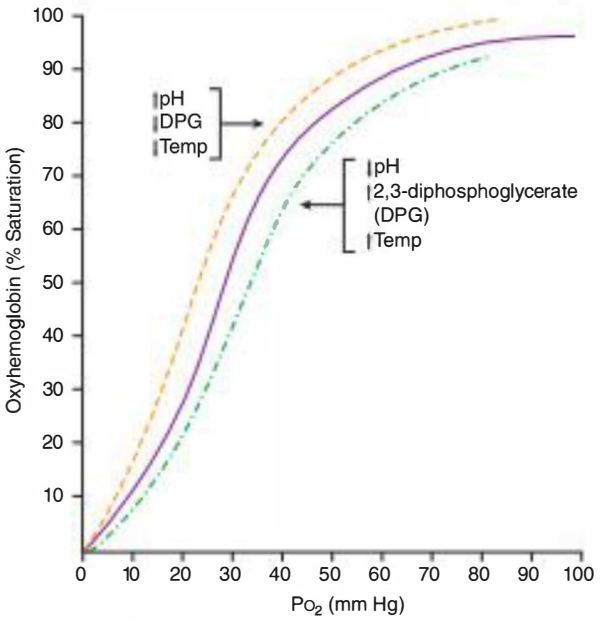
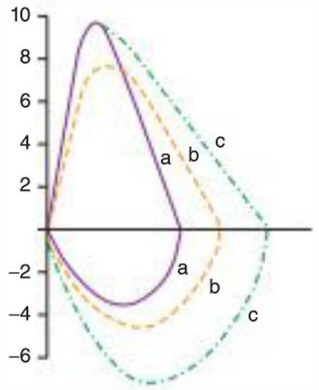


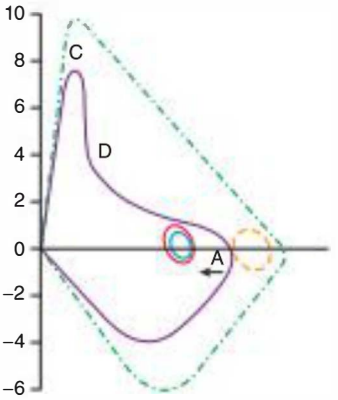

**FIGURE 3-2** Oxygen–hemoglobin dissociation curve.

## PREOPERATIVE PULMONARY FUNCTION TESTING

Spirometry was first used by John Hutchinson in 1848 and is the most common test performed in the pulmonary function laboratory. Spirometry measures the changes in volume and flow during tidal breathing, maximal forced expiration, and inhalation. The graphic interpretation of the test, the flow volume loop depicts both inspiration and expiration tracings. At least three tests are performed to ensure reproducible effort. Figure 3-3 shows the flow volume loops of a normal individual compared with the patterns seen in obstructive and restrictive lung disease. Spirometry provides several measurements that are important to understand, including the forced vital capacity (FVC), $FEV_1$, and $FEV_1$/FVC ratio. The FVC is a measure of the volume exhaled during the entire forced expiratory effort. The FVC is decreased in both obstructive and restrictive lung diseases. It can also be decreased as a result of chest wall deformities, pleural disease, or neuromuscular diseases. The $FEV_1$ measures the volume of gas exhaled in the first second of exhalation (Fig. 3-4). In restrictive lung disease, the $FEV_1$ is decreased in similar proportion to the FVC; therefore, the $FEV_1$/FVC ratio is normal or even increased. In contrast, patients with obstructive lung disease have difficulty emptying the air within the lungs because of an increased resistance to expiratory flow and a loss of elastic recoil, and the $FEV_1$ is decreased to a greater degree than the FVC. The expiratory flow limitation seen in obstructive lung disease leads to a characteristic decrease in the $FEV_1$/FCV ratio and a classic




Flow volume curve in restrictive airways disease, a: early stage of restrictive type, b: late stage of restrictive type, c: normal curve




Flow volume curve in peripheral airways obstruction C; Reduced PEFR, CD : Period of high flow, CA : Curvilinear shape.
Arrow : Tidal volume loop moving towards vital capacity.

**FIGURE 3-3** Flow volume loops in restrictive and obstructive lung disease as compared with normal. (From *Lung India* 1996;14(4):169–171. With permission.)

"scooped out" expiratory flow-volume loop. Spirometry is the only pulmonary function test needed to make the diagnosis of obstructive lung disease, and an $FEV_1$/FVC ratio of less than the fifth percentile of predicted is the diagnostic criterion of the American Thoracic Society (ATS).[14] After a diagnosis of airway obstruction has been made, the severity of obstruction is usually determined by the percent predicted of the $FEV_1$, as shown in Table 3-3.

Spirometry is suggestive of restrictive lung disease when both FVC and $FEV_1$ are decreased but the $FEV_1$/FVC ratio is normal; however, measured lung volumes (a distinct test) must demonstrate a decreased total lung capacity to make the diagnosis. Spirometry can also be ordered with and without the use of inhaled bronchodilators to determine the amount of reversible airway obstruction. Reversible airway obstruction is defined as greater than a 12 to 15 percent improvement in the $FEV_1$ or FVC after treatment with an

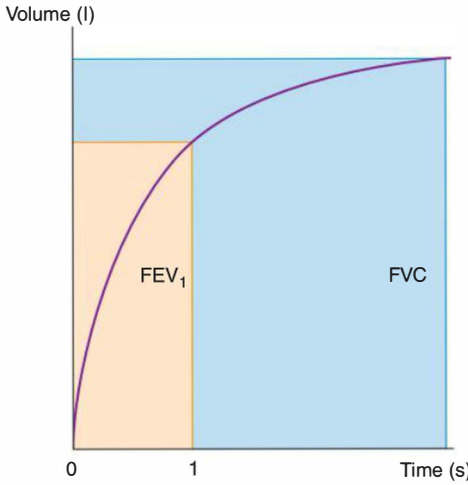



**FIGURE 3-4** Graphic representation of forced expiratory volume at 1 s ($FEV_1$) as related to forced vital capacity (FVC).

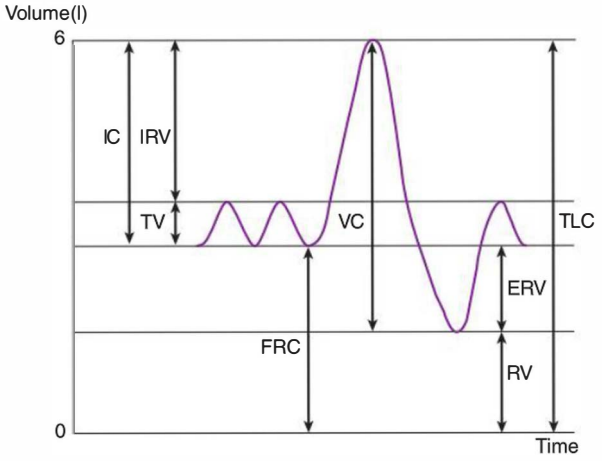



**FIGURE 3-5** Graphic representation of spirometric relationships. (From surgical tutor.org.) ERV, expiratory reserve volume; FRC, functional residual capacity; IC, inspiratory capacity; IRV, inspiratory reserve capacity; RV, residual volume; TLC, total lung capacity; TV, tidal volume; VC, vital capacity.

inhaled bronchodilator. The identification of patients with reversible airway obstruction can be an important component of a preoperative pulmonary evaluation, with a view to decreasing airway obstruction and minimizing surgical morbidity. Although spirometry is the most common of all the pulmonary function tests, more extensive testing of lung volumes or gas transfer is often needed.

Since spirometry measures only the volume of air exhaled (vital capacity, VC), it is unable to measure the residual volume (RV) or the total lung capacity (TLC). RV is the air left in the lung after a complete exhalation. TLC equals the RV plus the VC (Fig. 3-5). Several different techniques can be used to determine the TLC and RV. The three most common techniques to measure lung volume include inert gas dilution, nitrogen washout, and body plethysmography. A detailed discussion of each of these techniques is beyond the scope of this chapter; however, it is important to recognize that neither the inert gas technique nor the nitrogen washout technique measures the volume from poorly ventilated areas of the lung. Therefore, both these techniques can underestimate the TLC in patients with obstructive lung disease and air trapping, that is, patients with emphysema. Plethysmography will give an accurate measurement of lung volumes in these patients. As mentioned above, lung volumes are required to make the diagnosis of restrictive lung disease, which is defined by a TLC of less than 80 percent predicted and can result from a wide variety of causes, including pulmonary fibrosis, chest wall disorders, obesity, or neuromuscular disease. After confirming the presence of restriction, the VC is commonly used to quantify the severity of restriction, as shown in Table 3-4.

For patients with airway obstruction, the total lung capacity is usually normal or increased. Lung volumes are important for patients with airway obstruction and a decreased FVC to look for the presence of air trapping or coexistent restrictive lung disease. Air trapping is the inability to empty areas of the lung and consequent hyperinflation. Lung volumes in this setting demonstrate an elevated RV, greater than 130 percent predicted, and often an elevated TLC. A decreased TLC in the presence of airway obstruction indicates a combination of obstructive and restrictive disease. The combination of obstruction and restriction can make

**TABLE 3-3: Severity of Airflow Obstruction Based on $FEV_1$**

| $FEV_1$ | Severity of Obstruction |
|---|---|
| Greater than 70% predicted | Mild |
| 60–69% predicted | Moderate |
| 50–59% predicted | Moderately severe |
| 35–49% predicted | Severe |
| Less than 35% predicted | Very severe |

**TABLE 3-4: Severity of Restrictive Ventilatory Defect Based on Vital Capacity**

| Vital Capacity (VC) | Severity of Restriction |
|---|---|
| Greater than 60% predicted | Mild |
| 40–60% predicted | Moderate |
| Less than 40% predicted | Severe |

**TABLE 3-5: Typical Pulmonary Function Changes for Specific Diseases**

| Category | $FEV_1$/FVC | FVC | RV | DLCO |
|---|---|---|---|---|
| Asthma | Normal or ↓ | ↓ | Normal or ↑ | Normal |
| Emphysema | ↓ | Normal or ↓ | ↑ | ↓ |
| Chronic bronchitis | ↓ | ↓ | Normal | Normal |
| Interstitial lung disease | Normal or ↑ | ↓ | Normal | ↓ |
| Pulmonary hypertension | Normal | Normal | Normal | ↓ |
| Neuromuscular disease | Normal | ↓ | Normal or ↑ | Normal |

the determination of pulmonary function difficult to quantify but is important to recognize. Lung volumes are not indicated in all patients who undergo spirometry, but they can be useful in patients with a decreased FVC or in patients who are suspected of having restrictive lung disease of any cause.

The third most common test ordered from the pulmonary function lab is the diffusing capacity. It measures the transfer of gas from the air in the alveolar space to the hemoglobin of the red blood cells. Since it is technically difficult to measure the diffusion of oxygen, the pulmonary function lab measures the DLCO that closely mimics the transfer of oxygen and is used as a surrogate. A normal DLCO is approximately 20 to 30 mL/min/mm Hg and is influenced by age, sex, and height. Since the diffusion of gas is influenced by the oxygen-carrying capacity of blood, it is important to recognize the presence of anemia, which can significantly lower the measured DLCO. Pathologic conditions that can lower the DLCO to less than 80 percent predicted include pulmonary fibrosis, emphysema, pulmonary hypertension, right-to-left intracardiac shunt, and anemia. A few rare conditions can elevate the DLCO (greater than 130 percent predicted), which include asthma, alveolar hemorrhage, mild congestive heart failure (CHF), and left-to-right intracardiac shunt. The combination of spirometry, lung volumes, and DLCO can provide a wealth of information about the pathophysiology of lung diseases. Table 3-5 depicts the expected changes seen in different lung diseases.

In summary, the measurement of pulmonary function is readily available, minimally invasive, and can provide a large amount of information that can influence the perioperative and intraoperative management of patients with lung disease. It is important to remember that borderline pulmonary function tests should not exclude a patient from surgery if he or she is otherwise a good surgical candidate. More extensive exercise testing may be useful in patients with borderline pulmonary reserve who are being considered for lung resection.

## EXERCISE TESTING

Exercise testing can be used in a variety of clinical settings, including the assessment of patient suitability for lung resection. In this setting, exercise testing has been advocated for patients at moderate-to-high surgical risk whose pulmonary function, based on the preliminary evaluations, does not suggest adequate pulmonary reserve. Specifically, exercise testing may be useful in patients with obstructive lung disease and those with a postoperative predicted $FEV_1$ less than 1 L. It may also be informative in evaluating patients with a combination of obstructive and restrictive lung disease. Exercise testing can take several different forms. Simple tests such as the 6-min-walk or the stair-climb test have been evaluated in a small series of patients undergoing thoracotomy for lung cancer and have been shown to predict operative morbidity and mortality. During the 6-min-walk test, the subject walks on level ground at a brisk pace for 6 min and the distance covered is measured in feet. A stair-climb test measures the number of steps an individual can climb at a normal pace. One small study showed that a 6-min-walk distance of less than 1000 ft was predictive of complications within 90 days, with a positive predictive value of 85 percent and a negative predictive value of 100 percent. A stair-climb test result of less than 44 steps was also useful, with a positive predictive value of 91 percent and a negative predictive value of 80 percent.[28] The shuttle walk test has recently been validated to linearly correlate with $\dot{V}O_{2max}$, with a shuttle distance of 250 m, being equivalent to a $\dot{V}O_{2max}$ of 15 mL/kg/min.[15] For centers where formal CPET facilities are not easily accessible, these simple tests may be useful in carefully selected patients.

For most medical centers, more extensive testing can be performed with CPET, which offers the opportunity to measure the cellular, respiratory, and cardiovascular responses to exercise. CPET is underused because of a common lack of understanding of the test and the interpretation of the clinical information that it provides. There are a wide range of clinical situations in which CPET can be helpful. These include assessment of unexplained dyspnea or fatigue, disability evaluation, monitoring of response to treatment or rehabilitation programs, transplant evaluations, and preoperative risk assessment. To perform the test, a subject exercises on a stationary bike or treadmill, which calculates the work performed. While exercising, the individual is connected to a continuous electrocardiogram to monitor for arrhythmias or signs of myocardial ischemia. In addition, gas exchange is measured including oxygen ($O_2$) consumption and carbon dioxide ($CO_2$) production. Also spirometry

and ABG measurements can be obtained before, during, and after exercise. A complete discussion of the interpretation of CPET is beyond the scope of this chapter, and has been recently reviewed elsewhere.[32]

Some of the more useful physiologic measurements provided by CPET are discussed briefly below. The most basic measurements include responses to graded exercise in terms of blood pressure, heart rate, and respiratory rate. The frequent monitoring of vital signs can provide important information regarding the cardiovascular response to stress. Blood pressure and heart rate are measured every several minutes or continuously via an arterial catheter. Normal individuals should be able to exercise to a heart rate of greater than 80 percent of the predicted maximal heart rate. In an individual who is unable to reach 80 percent of maximum heart rate without reaching other limits, physical deconditioning may be the cause of dyspnea. The normal blood pressure response to exercise is a moderate increase. Large increases or inappropriate decreases in blood pressure with graded exercise can help to identify cardiovascular pathology. Spirometry can also be performed as part of CPET. It is often performed before and after CPET. Decreases in $FEV_1$ and $FEV_1$/FVC can identify exercise-induced bronchospasm as a cause of dyspnea.

Most of the data provided by CPET are obtained from the measurement of exhaled gas. These measurements are interpreted in the context of the work being performed on the stationery bike or treadmill, which is recorded as well. One of the more useful measurements provided by CPET is the maximal oxygen uptake during graded exercise ($\dot{V}O_{2max}$). Oxygen consumption is determined by the cardiac output, arterial oxygen content, and extraction of oxygen by the tissues. In interpreting a CPET, $\dot{V}O_2$ is one of the first results to look at because it indicates whether the patient's physiologic responses allow him or her to reach maximal aerobic function. A subject who is unable to reach 80 percent $\dot{V}O_{2max}$ with exercise is considered to have exercise limitation. If the aerobic function is limited, reflected in a $\dot{V}O_{2max}$ less than 80 percent predicted, other measurements can be used to determine the cause of the limitation. As stated earlier, $\dot{V}O_{2max}$ is also the most studied value for predicting surgical risk, especially for patients undergoing lung resection surgery.

For patients who are identified as having exercise limitations, CPET can be helpful in determining the etiology. Except for highly trained athletes, normal individuals are cardiac-limited in response to exercise. This limitation is indicated when the heart rate (HR) reaches above 80 percent of the predicted maximum. Most normal subjects have a ventilatory reserve of approximately 10 L/min or 10 to 30 percent of the ventilatory capacity. The maximum ventilatory capacity is predicted by using the maximum voluntary ventilation (MVV) determined by spirometry. The percent of ventilatory capacity reached with exercise is calculated by dividing the $\dot{V}_E$ by the MVV. An individual has reached his or her ventilatory limits when $\dot{V}_E$/MVV is greater than 80 percent. In addition to ventilatory limits, the respiratory system can be limiting because of problems with gas exchange or $\dot{V}$/Q mismatching. Several different measurements can be used to identify problems with gas exchange. The arterial $P\dot{O}_2$ normally increases with exercise owing to improved $\dot{V}$/Q matching and increasing $\dot{V}_E$. Abnormal responses to exercise include a decrease in arterial $PO_2$ or an increase in the A–a gradient. The arterial $P\dot{C}O_2$ normally decreases with exercise owing to the increased $\dot{V}_E$. An increase in the $P\dot{C}O_2$ with the increasing $\dot{V}_E$ seen with exercise is indicative of an abnormal increase in the dead space/tidal volume ratio ($\dot{V}_D/\dot{V}_T$). Abnormalities in gas exchange can be due to pathologies within the lung parenchyma or pulmonary vascular disease.

Another value that is frequently reported is the anaerobic threshold (AT). AT is the $\dot{V}O_2$ during exercise where aerobic metabolism is supplemented with anaerobic metabolism. The level is reflected by an increase in the lactic acid within the blood. Several different methods can be used to identify the AT. For patients with arterial catheters, frequent blood sampling can be performed to measure blood lactate levels. More commonly, the AT is extrapolated from measures of exhaled gas. The switch from aerobic to anaerobic metabolism leads to a cascade of physiologic events. Increasing blood lactate leads to a decrease in arterial pH, consumption of bicarbonate, and subsequent increase in $\dot{C}O_2$ production. This is reflected in a nonlinear increase in $\dot{V}O_2$ once the subject passes the AT. The acidosis also causes an increased ventilatory drive and an increased $\dot{V}_E$. A graph of $\dot{V}CO_2$ and $\dot{V}_E$ can be used to extrapolate the AT. The AT can be used to estimate the amount of exercise or work that an individual can perform for a sustained time period.

Finally, another useful measurement provided by CPET is the $O_2$ pulse, which is calculated by dividing the $\dot{V}O_2$ by the HR. It also is equal to the stroke volume (SV) multiplied by the arterial to mixed venous oxygen content difference $[c(a-v)O_2]$.

$$O_2 \text{ pulse} = \dot{V}O_2/HR = SV * c(a-v)O_2$$

With exercise, the $O_2$ pulse normally increases, mainly owing to increasing oxygen extraction by the muscles and increasing $c(a-v)O_2$. The $O_2$ pulse decreases and reaches its maximum at low levels of work in several settings, including CHF, anemia, arterial hypoxia, or elevated carboxyhemoglobin levels. These are just a few of the physiologic measurements provided by CPET. When used in the correct setting and interpreted by knowledgeable physicians, they can be extremely useful in a number of clinical settings.

## THE ROLE OF BRONCHOSCOPY IN THORACIC SURGERY

Lung cancer is the leading cause of cancer deaths in the United States, and will account for approximately 157,300 deaths in 2010, more than colon, breast, and prostate cancers combined.[16] It is estimated that 222,520 new cases of lung cancer will be diagnosed in 2010, and the incidence and number

of lung cancer deaths continues to increase amongst women in the United States.[17] It is estimated that over 90 percent of all lung cancer deaths in the United States each year are directly caused by tobacco abuse.[18] Bronchoscopy provides a minimally invasive approach for the diagnosis of mediastinal and hilar adenopathy, tumors in the central airway, and solitary parenchymal lesions. Advances in navigation such as electromagnetic and virtual bronchoscopic navigation (to be discussed later) have significantly improved the yield for peripheral tumors. Given the minimally invasive nature of the procedure, bronchoscopy is also an invaluable tool to the surgeon and pulmonologist for both the diagnosis and the management of airway tumors and disorders.

## STAGING SYSTEM FOR LUNG CANCER

The initial workup and diagnostic testing for lung cancer is focused on appropriate staging of the disease. Prognostic data including response to treatment and survival as well as guidance for treatment management have all been closely linked with appropriate staging of the disease. Lung cancer staging and pathology is divided into two main diagnostic groups: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)

The staging of NSCLC is defined by the TNM system. The tumor characteristics (T) focus on tumor size and presence and extent of tumor invasion into surrounding structures. Lymph node involvement (N) is defined as the presence or absence of metastasis to regional lymph nodes in defined anatomic locations. The distant metastasis criteria (M) is simply the presence or absence of distant metastatic disease or malignant pleural disease.[19,20] The TNM staging system is used to determine the clinical-diagnostic stage, surgical-pathologic stage, re-treatment stage, and autopsy stage as defined above.

The classic staging of SCLC is a two-stage system defined by limited or extensive stage disease. Limited disease is defined by a disease burden that is within a single radiation therapy portal window and found within the ipsilateral hemithorax. Extensive disease is defined by tumor burden beyond the ipsilateral hemithorax.[21]

## STAGING IMPLICATIONS ON TREATMENT AND SURVIVAL IN NSCLC

Using the TNM data, patient groups can be further classified into TNM subset groups. Each main group in this classification schema has similar treatment modalities and survival data. Unfortunately, the overall results of treatment response in NSCLC patients remain poor except for localized disease.[22] Surgical resection of patients with Stage I–IIb portends a better prognosis and the highest chance of potential cure. Radiation therapy has curative intent in a minority of NSCLC patients and is mostly used in conjunction with chemotherapy and/or palliation. Chemotherapy has multiple roles in the treatment of NSCLC from neoadjuvant chemotherapy and radiation prior to surgery, adjuvant therapy after resection, to palliation.[23] The 5-year survival in patients with NSCLC correlates well with the clinical and pathological stage. Patients with Stage IA disease have a median survival of 58 months whereas patients diagnosed with Stage IV disease have a median survival of only 6 months.

The clear relationship between staging and response to treatment and survival has made proper diagnostic testing and sampling crucial in the diagnosis and treatment of lung cancer. Clinical or noninvasive staging can markedly differ from pathologic staging. It has been shown that up to 24 percent of patients are clinically overstaged and 20 percent are understaged when compared with pathologic data.[24] As a result of these types of discrepancies with their obvious repercussion, the major US and European societies have published guidelines suggesting that all patients should have appropriate pathologic staging prior to undergoing cancer resection with curative intent.

## INVASIVE STAGING FOR NSCLC

Based on the TNM staging system, patients in whom distant metastatic disease has been investigated and found to be absent, the status of nodal metastasis within the mediastinum is the next level of investigation that is needed to accurately stage the patient. To accomplish this, there are several invasive procedures available to the clinician. The primary goal of each procedure is to obtain adequate tissue from within the mediastinal lymph nodes to accurately perform pathologic staging.[25] Regional lymph nodes within the mediastinum are classified by the nodal TNM system (Fig. 3-6). Station 1 nodes or high mediastinal nodes are found lying above a horizontal line at the upper rim of the brachiocephalic (left innominate) vein where it ascends to the left, crossing in front of the trachea at its midline. Station 2 nodes or the upper paratracheal nodes are located lying above a horizontal line drawn tangential to the upper margin of the aortic arch and below the inferior boundary of Station 1 nodes. Station 3 nodes or the prevascular and retrotracheal nodes may be designated 3A (anterior) and 3P (posterior). Station 4 nodes or the lower paratracheal nodes on the right lie to the right of the midline of the trachea between a horizontal line drawn tangential to the upper margin of the aortic arch and a line extending across the right main bronchus at the upper margin of the upper lobe bronchus, and contained within the mediastinal pleural envelope; the lower paratracheal nodes on the left includes nodes to the left of the left lateral border of the trachea, medial to the ligamentum arteriosum. Station 5 nodes (subaortic or aortopulmonary window nodes) are lateral to the ligamentum arteriosum or the aorta or left pulmonary artery and proximal to the first branch of the left pulmonary artery and lie within the mediastinal pleural envelope. Station 6 nodes are lying anterior and lateral to the ascending aorta and the aortic arch or the

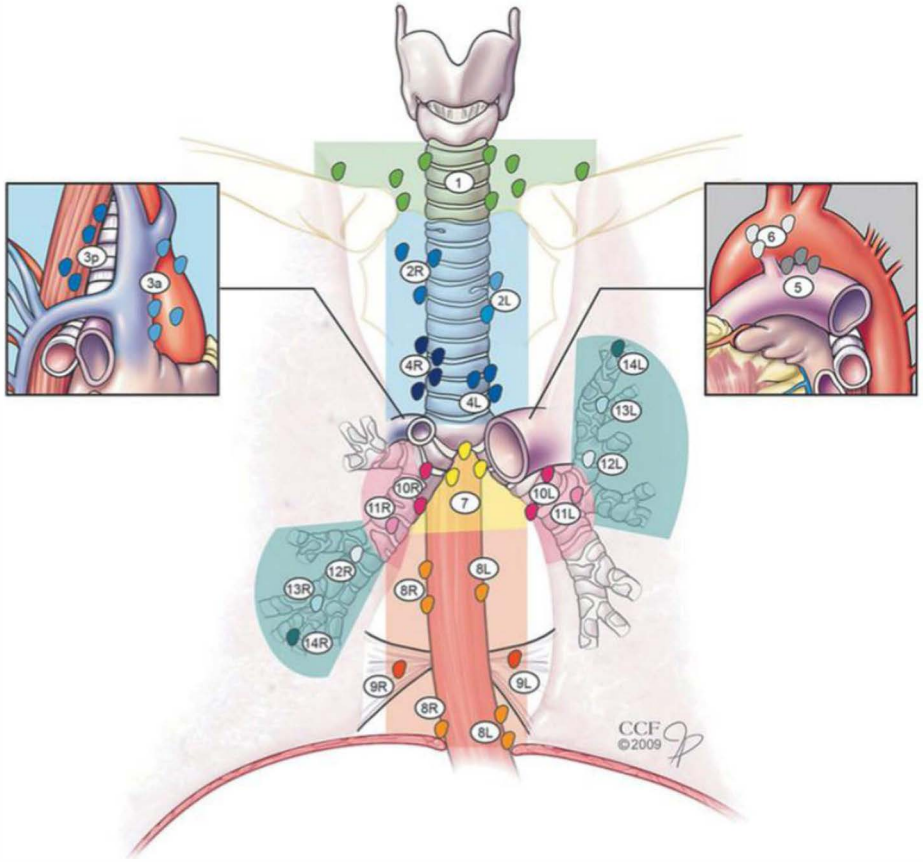



**FIGURE 3-6** Lymph node map: lymph node zones are supraclavicular (green), upper mediastinal (blue), aortopulmonary (gray), subcarinal (yellow), lower mediastinal (orange), hilar/interlobar (pink), and peripheral (aqua). (Reprinted with permission from Cleveland Clinic Center for Medical Art and Photography © 2009–2013. All rights reserved.)

innominate artery, beneath a line tangential to the upper margin of the aortic arch. Station 7 is found caudal to the carina of the trachea, but not associated with the lower lobe bronchi or arteries within the lung. Station 8 nodes lie adjacent to the wall of the esophagus and to the right or left of the midline, excluding subcarinal nodes. Station 9 nodes are located within the pulmonary ligament, including those in the posterior wall and lower part of the inferior pulmonary vein.[26,27]

N1 nodes are defined as peribronchial, intrapulmonary, or hilar nodes located on the ipsilateral side of the primary tumor. N2 nodes are located ipsilateral to the primary tumor within the mediastinal and subcarinal region. N3 nodes are found within the contralateral hilar/mediastinal and ipsilateral or contralateral scalene or supraclavicular regions.

Mediastinoscopy is currently considered the 'gold standard' for mediastinal staging. The procedure allows access to lymph nodes located in nodal Stations 2, 4, and the anterior component of Station 7. The sensitivity of mediastinoscopy ranges between 78 and 98 percent with a specificity of 100 percent. Despite direct visualization of lymphatic tissue and resection there is still a 9 to 11 percent false negative rate.[28] The limits of the procedure are that routine lymph node sampling during a mediastinoscopy does not allow access to Stations 5, 6, posterior 7, 8, and 9.[29] An anterior mediastinoscopy (Chamberlain procedure) can allow sampling of nodal Stations 5 and 6. Although mediastinoscopy is generally a same-day procedure, it is performed in under general anesthesia, has a mortality of 0.2 percent with a morbidity reported up to 2.5 percent, and has considerable cost. It is a surgical procedure performed on a subset of patients who may be deemed nonoperable for eventual surgical resection.[28] Despite current recommendations, mediastinoscopy is performed only in 27 percent of patients undergoing lung cancer surgery. Successful sampling of nodal tissue is variable and nodal tissue is obtained less than 50 percent of the time.[30]

Bronchoscopy provides a minimally invasive approach for the diagnosis of tumors in the central airways. The bronchoscopic evaluation of patients with suspected malignancy is guided by clinical symptoms as well as radiographic findings. Depending upon the history and chest computed tomography (CT)/PET-CT findings, bronchoscopy may be

the diagnostic modality of choice as it can both make the diagnosis and stage the patient at the same sitting. If appropriate staging is to be performed, biopsy of the lesion that will place the patient in the highest stage should occur prior to other biopsies. For example, if a patient presents with a left lower lobe mass, an enlarged subcarinal (Station 7), and right paratracheal (Station 4R) lymph node, the appropriate procedure would be a bronchoscopy with sampling of the 4R node as this would stage the patient with N3 disease, making the patient unresectable. Initial biopsy of the mass could contaminate the working channel and make the sample a false positive, precluding the patient from potentially curative surgery.

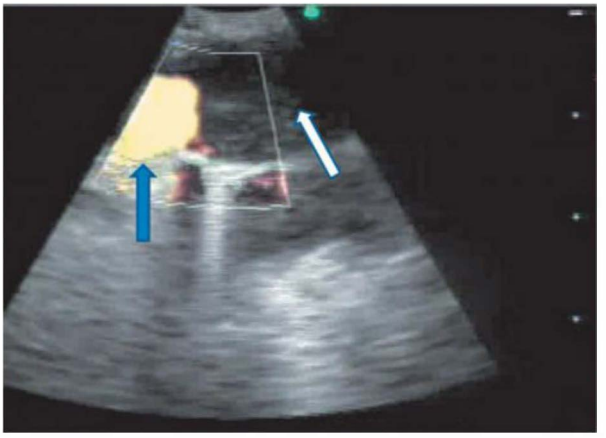


**FIGURE 3-7** EBUS ultrasound image of lymph node (white arrow) and surrounding blood vessel (blue arrow).

## ENDOBRONCHIAL ULTRASOUND-GUIDED TRANSBRONCHIAL NEEDLE ASPIRATION

Transbronchial needle aspiration (TBNA) is a biopsy technique used during bronchoscopy that involves passing a catheter containing a needle through the tracheal or bronchial wall into lymph nodes or masses to obtain samples for cytopathologic assessment. The procedure is performed in the outpatient setting with moderate sedation. TBNA has been shown to be an effective means of both diagnosing and staging lung cancer. Unlike mediastinoscopy, nodal Stations 2, 3, 4, 7, 10, and 11 are generally accessible with TBNA. The procedure is minimally invasive, safe, and less costly than mediastinoscopy and has been shown to preclude surgery in up to 29 percent of patients.[31]

Recent advances in TBNA have integrated ultrasound technology with bronchoscopy allowing direct visualization of mediastinal structures that has greatly improved the yield. In 2005, the convex probe endobronchial ultrasound (EBUS) bronchoscope was first introduced in Japan. The bronchoscope has an ultrasound transducer at the tip as well as a video processor to allow for both a live ultrasound and optical image. This newer technology provides a distinct advantage by allowing for real-time visualization of the targeted lymph node through the airway wall with ultrasound technology. Real-time imaging of the needle sampling of the target lymph node (white arrow) can then be achieved through the working channel of the bronchoscope with a dedicated needle system. Additionally, mediastinal vessels can also be visualized (blue arrow), decreasing the incidence of inadvertent puncture (Fig. 3-7).

Although the convex EBUS system has only been available since 2005, it has made a significant impact on the practice and yield of diagnostic testing for mediastinal staging of lung cancer. In a recent study of 572 lymph nodes in 500 patients, EBUS-TBNA was shown to have a diagnostic yield of 94 percent.[32]

Because of the success and impact of EBUS-TBNA on lung cancer staging, data are now emerging directly comparing the gold standard of mediastinoscopy to EBUS-TBNA for mediastinal staging. A recent prospective, crossover trial with surgical lymph node dissection compared biopsy results of paratracheal and subcarinal lymph nodes in patients undergoing EBUS-TBNA and then mediastinoscopy. In the 66 patients studied, the prevalence of malignancy was 89 percent. EBUS had a higher overall diagnostic yield (91%) compared with mediastinoscopy (78%; $p = 0.007$) in the per lymph node analysis. The sensitivity, specificity, and negative predictive value of EBUS were 87, 100, and 78 percent, respectively. The sensitivity, specificity, and negative predictive value of mediastinoscopy were 68, 100, and 59 percent, respectively. No significant differences were found between EBUS (93%) and mediastinoscopy (82%; $p = 0.083$) in determining true pathologic N stage (per patient analysis).

Although data are favorable, it is important to recognize the limitations of a needle aspirate in that a nondiagnostic test with EBUS-TBNA should not be considered a negative test. If a nondiagnostic result is obtained, confirmatory tissue with mediastinoscopy or by video-assisted thoracic surgery (VATS) is required.[33]

## EBUS FOR RESTAGING THE MEDIASTINUM

Recent data in the oncologic literature have suggested that there may be a role for surgical resection in NSCLC patients who are initially Staged IIIA–N2 and have a favorable response to induction chemotherapy or chemoradiotherapy (neoadjuvant therapy). These patients may be successfully downstaged allowing for resection with curative intent. Accurate restaging of these patients after induction therapy can be challenging. Previously, the standard of care was to attempt restaging with mediastinoscopy. Unfortunately, performing a repeat mediastinoscopy, especially after radiation therapy, can be technically difficult due to scar tissue formation, adhesions, and bleeding.[34,35] It has also been shown that due to these technical challenges the yield of diagnostic tissue sampling during repeat mediastinoscopy decreases.[36]

As a result of the technical challenges associated with repeat mediastinoscopy, some experts currently recommend EBUS-TBNA for initial staging and mediastinoscopy for restaging of the mediastinum, with the understanding that the sensitivity, specificity, and overall accuracy seems to be less for restaging when compared with data on initial staging.[37]

## EBUS AND EUS TBNA: FULL ENDOSCOPIC STAGING

Both EBUS and EUS (esophageal ultrasound) allow for successful sampling of mediastinal lymph nodes but each have certain limitations. EUS fine needle aspiration (FNA), performed with a specialized gastroscope through the GI tract, allows for access to Stations 4R, 4L, 5 (potentially), 7, 8, and 9. In addition, EUS allows access to the left adrenal gland, which could therefore evaluate for Stage 4 disease. By using EBUS-TBNA and EUS-FNA during the same procedure, studies have shown a combined approach yielding a sensitivity of 93 percent and a negative predictive value of 97 percent. In this study, the combined modalities also yielded better results than either procedure alone.[38]

## BRONCHOSCOPIC SAMPLING OF PARENCHYMAL ABNORMALITIES

EBUS can also be used to help improve the accuracy of sampling peripheral nodules. The earliest EBUS system used a radial probe with a 20 MHz transducer that could be inserted via a 2.8 mm working channel. Despite not allowing for real-time guidance, the early studies with radial probe EBUS found significant improvements in the yield of sampling of peripheral nodules. The sonographic characteristics of peripheral nodules have also been shown to correlate well with histology.

There are several available tools by which to obtain specimens during bronchoscopy including forceps biopsy, brushing, bronchial wash/lavage, and TBNA. To perform a bronchoalveolar lavage (BAL), the bronchoscope is wedged in the target segmental or sub-segmental bronchus leading to the lesion. Aliquots of normal saline solution are instilled, and then aspirated. BAL is thought to sample approximately 1 million alveoli, and the cellular and noncellular contents of the lavage fluid have been shown to closely correlate with the inflammatory nature of the entire lower respiratory tract.[39-42] The use of multiple sampling modalities has been shown to improve the yield as compared with using only one method to sample parenchymal nodules/masses.

## ENHANCED NAVIGATION

The use of electromagnetic navigation, especially when used in conjunction with radial probe EBUS, is a novel technology that has been shown to allow accurate sampling of peripheral solitary pulmonary nodules <2 cm in diameter.[43] A virtual bronchoscopy is generated from the patients CT scan. The patient lies in an electromagnetic field and a steerable guide is placed through an extended working channel. A bronchoscopic registration is then performed, which in essence, fuses the CT scan with the patient's anatomy. Navigation to the target then occurs by looking at the CT in the axial, sagittal, and coronal planes. Once found, the guide is removed, and standard bronchoscopic tools such as TBNA needles, forceps, and brushes are placed through the extended working channel.

## RIGID BRONCHOSCOPY AND ADVANCED BRONCHOSCOPIC TECHNIQUES

Although many advanced techniques can be performed with flexible bronchoscopy, the rigid bronchoscope remains the tool of choice for therapeutic interventions.[44,45] The rigid bronchoscope provides an airway in which to oxygenate/ventilate the patient as well as pass multiple devices including large-bore suction catheters, laser/argon plasma coagulation (APC)/electrocautery fibers, the microdebrider blade, and larger biopsy instruments. The rigid bronchoscope itself can also be used to achieve relative lung isolation, dilate stenosis, and "core-out" tumor from the central airways.

### Argon Plasma Coagulation

APC is a noncontact method using ionized argon gas (plasma) to achieve tissue coagulation and hemostasis. As the plasma is directed to the closest grounded source, APC has the ability to treat lesions lateral to the probe. The depth of penetration for APC is approximately 2 to 3 mm; hence, the risk of airway perforation is less when compared with lasers.

### Laser Therapy

The Nd:YAG (neodymium:yttrium aluminum garnet) laser remains the most widely used laser in the lower respiratory system, and has been used for both benign and malignant disease.[46] In addition, newer lasers, the Nd:YAP (yttrium–aluminum–perovskite) and the $CO_2$ laser with a flexible catheter, have been introduced and are available. The primary advantage of laser photoresection is that it provides rapid destruction/vaporization of tissue. Care must be taken however, as the depth of penetration can approach 10 mm, and airway perforation with resultant pneumothorax, pneumomediastinum, and vascular injury has been reported. Despite this, the safety record of laser bronchoscopy is excellent, with an overall complication rate of less than 1 percent.[46] Lesions most amenable to laser therapy are central, intrinsic, and short (<4 cm), with a visible distal endobronchial lumen.[47]

When lesions meet these criteria, patency can be re-established in more than 90 percent of the cases.

## Electrocautery

Electrocautery uses alternating current at high frequency to generate heat, which cuts, vaporizes, or coagulates tissue depending on the power. Electrocautery is a contact mode of tissue destruction and a variety of cautery probes are available including blunt-tip probes, knives, and snares. The snare is an ideal tool for pedunculated lesions as the stalk can be cut and coagulated while preserving the majority of the tissue for pathologic interpretation.[48] The knife is also an excellent tool for producing radial incisions prior to dilation of web-like tracheal stenosis. As with laser therapy, the risks of electrocautery include airway perforation, airway fires, and damage to the bronchoscope.

## Microdebrider

Mechanical debridement of endobronchial tumor and granulation tissue can be accomplished with various modalities. Microdebriders are powered instruments that consist of a hollow shaft with a rapidly rotating blade and suction. The device has been used for many years by the otolaryngology community for sinus surgery and other modalities.[49] More recently, the procedure has been used as an alternative to or in conjunction with other modalities such as laser excision or electrocautery. Airway debulking with the microdebrider is accomplished by shaving and suctioning tissue under direct telescopic guidance through the rigid bronchoscope.[50]

The microdebrider requires a rigid bronchoscope or laryngoscope, and due to its rigid structure, it is not amenable to the flexible bronchoscopic technique. Although the technology appears promising and a useful modality in the management of central airway obstruction (CAO), further studies are required to assess the long-term outcomes of the microdebrider compared with more conventional therapy.

## Airway Stents

Montgomery is credited as initiating the widespread use of airway stents after his development of a silicone T-tube in 1965 for use in patients with tracheal stenosis.[51] Dumon, however, introduced the first completely endoluminal airway stent in 1990.[52] Airway stents are the only technology that can alleviate extrinsic airway compression. They are commonly used in conjunction with the other modalities for patients with intrinsic or mixed disease.

Over the past 15 years, there has been an explosion in both stent design and the number of endoscopists who place airway stents. As with any procedure, it is crucial to understand the indications and contraindications of the procedure as well as be able to anticipate, prevent, and manage the associated complications. Unfortunately, the "ideal stent" has not yet been developed. This stent would be easy to insert and remove, yet not migrate; of sufficient strength to support the airway, yet be flexible enough to mimic normal airway physiology and promote secretion clearance; biologically inert to minimize the formation of granulation tissue; and available in a variety of sizes.

There are currently two main types of stents: metal, generally made of nitinol, and silicone. Although metal stents are easily placed, they can be extremely difficult to extract. They are available in covered (typically with silicone or polyurethane) and uncovered varieties. For malignant airway obstruction, the only appropriate metal stents are covered models, which minimize tumor in growth. Some authors feel that there is no indication for an uncovered metal stent. The over-use of metallic stents in patients with nonmalignant airway obstruction has led to the FDA creating a black-box warning recommending their use as a modality of last resort in these patients.[53] The main advantage of metal stents is their larger internal:external diameter ratio as compared with silicone stents. Although silicone stents require rigid bronchoscopy for placement, they are more easily removed and are significantly less expensive.

## Complications During Bronchoscopy

Bronchoscopy is generally considered a relatively safe procedure.[54] That being said, it is common that patients in whom bronchoscopy is performed can have multiple comorbidities and the bronchoscopist needs to be aware of the patient's medical history including medications and allergies. In addition, the bronchoscopist needs to have a thorough understanding of the effects and side-effects of the medications they will use to achieve adequate topical anesthesia and moderate sedation and be skilled in airway management should the patient experience hypoxemia/hypercapnia. Transient fever is the most common adverse event following BAL, and can be seen in up to one-third of patients. Major adverse events including hypoxemia, pneumothorax, bleeding, and death may also occur, and both patient and procedure-related factors are important determinants. The British Thoracic Society has published its recommendations concerning the performance of diagnostic flexible bronchoscopy and includes steps that should be taken to minimize complications.[54]

## SUMMARY

Cardiothoracic surgery can be associated with a high rate of pulmonary complications due to the high-risk nature of the surgical procedures and also because most of the patients have underlying lung disease. The preoperative evaluation can risk stratify which patients can safely undergo these potentially lifesaving surgical procedures with minimal risk

of morbidity and mortality. By understanding both the preoperative evaluation algorithm and role for bronchoscopy in the preoperative workup, the number of patients who are offered surgery safely can be maximized and the complications limited.

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## PULMONARY PHYSIOLOGY, FUNCTION TESTS, AND BRONCHOSCOPIC TECHNIQUES BOARD REVIEW QUESTIONS (CHAPTER 3)

1. Which of the following is the most specific predictor of postoperative complications following lung resection?
   A. $FEV_1$ less than 0.8 L
   B. DLCO less than 40% predicted
   C. Elevated A–a gradient
   D. $P\dot{C}O_2$ greater than 44 mm Hg
   E. $V\dot{O}_{2max}$ less than 10 mL/kg/min
2. Which of the following elevates DLCO?
   A. Emphysema
   B. Pulmonary hypertension
   C. Congestive heart failure
   D. Anemia
   E. Pulmonary fibrosis
3. Which of the following lymph node stations is incorrect?
   A. Station 1: above brachiocephalic vein
   B. Station 9: within pulmonary ligament
   C. Station 6: anterior and lateral to ascending aorta
   D. Station 4L: left of lateral border of trachea
   E. Station 7: cephalad to carina
4. Which of the following nodes is best accessed by a Chamberlain procedure?
   A. Station 2
   B. Station 4
   C. Station 6
   D. Station 8
   E. Station 10
5. Endobronchial ultrasound has been demonstrated to be superior to mediastinoscopy for staging in all of the following except?
   A. Sensitivity
   B. Specificity
   C. Negative predictive value
   D. Overall diagnostic yield

## ANSWERS

1. **Answer: E.** Maximal exercise testing is the most specific predictor of postoperative complications.
2. **Answer: C.** Congestive heart failure elevates DLCO; the other conditions reduce DLCO.
3. **Answer: E.** Station 7 nodes are caudal, not cephalad, to the carina.
4. **Answer: C.** Station 6 nodes (aortopulmonary window) are best accessed via left anterior thoracotomy, or Chamberlain procedure.
5. **Answer: C.** Endobronchial ultrasound has been demonstrated to be superior to mediastinoscopy for staging except in specificity, in which the two modalities are equivalent.

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# 4

# Congenital Pulmonary Disorders

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**KEY CONCEPTS**

- Epidemiology
  - Congenital pulmonary anomalies include a multitude of clinical entities linked by a common developmental lineage. The prevalence is dependent upon the particular malformation. These anomalies represent different variations of shared embryologic pathways and therefore possess clinical similarities and occasionally present simultaneously.
- Pathophysiology
  - Physiologically, the impact of these lesions, which can be mild or detrimental, depends largely on two factors—pulmonary hypoplasia and fetal hydrops. The mass effect of fetal intrathoracic lesions can impair lung development and decrease cardiac output secondary to mediastinal shift, causing fetal demise or severe compromise. Lesions that replace functional lung parenchyma can also cause pulmonary insufficiency.
- Clinical features
  - Many congenital pulmonary anomalies present postnatally with frequent pulmonary infections, respiratory distress, and hemoptysis, although others are discovered incidentally on plain chest radiography. Diagnoses of congenital pulmonary malformations are now typically detected with prenatal surveillance imaging.
- Diagnostics
  - Prenatal ultrasound is the primary diagnostic modality whereby congenital pulmonary anomalies are identified in utero and the degree of hydrops is assessed. Postnatally, computed tomography or magnetic resonance imaging can be used to differentiate lesions based on anatomic characteristics; but since surgical resection is the treatment for most mass lesions, additional imaging is of value to ensure the prenatal lesion has not regressed.
- Treatment
  - Resection often is curative for focal lesions, but outcome is ultimately dependent on residual pulmonary function and associated medical conditions. Fetal intervention is being offered as an alternative for some congenital pulmonary anomalies, although outcomes have been mixed.
- Outcomes
  - Outcomes depend on the particular disease process. Generally, excellent survival rates are noted with timely treatment of bronchogenic cysts, pulmonary sequestration, and congenital lobar emphysema. A large percentage of congenital pulmonary adenomatoid malformations postnatally do regress. The prognoses of other entities are adversely affected by the presence of fetal hydrops prenatally or the association of recurrent infections or malignant risk in some of the anomalies.

## INTRODUCTION

Congenital lung malformations represent a diverse spectrum of developmental defects. A high index of suspicion for these relatively rare malformations is essential in evaluating a thoracic lesion in a child. The clinical presentation is variable, presenting as respiratory distress in a newborn or remaining asymptomatic until adolescence or even adulthood. The revolution in prenatal imaging, with the ubiquity of antenatal ultrasound, has enabled earlier and more frequent detection of pulmonary anomalies: The most commonly identified prenatal pulmonary anomaly remains the cystic lung lesion with an estimated incidence of 1 in 8300 to 35,000 births.[1,2] Prenatal characteristics such as

**TABLE 4-1: Characteristics of Congenital Pulmonary Malformations**

| Type | Typical Presentation | Anomaly | Associations |
|---|---|---|---|
| Bronchogenic cyst | Mediastinal location, asymptomatic | Abnormal bronchial budding | – |
| Peripheral pulmonary cyst | Respiratory distress in infants[a] | Abnormal alveolar development | – |
| Congenital lobar emphysema | Acute respiratory distress in neonate (LUL > RML) | Hyperinflation associated with cartilage deficiency | 20% cardiac anomalies |
| Pulmonary sequestration | Antenatally/incidentally detected | – | Anomalous blood supply from aorta; potential GI tract communication |
| Extralobar (25%) | Neonate; dyspnea or difficulty feeding | Separate lobe and pleura | |
| Intralobar (75%) | Later recurrent pneumonias[a] | Intraparenchymal | |
| **CPAM[b] Type (Prevalence)** | **Typical Presentation** | **Cyst size/Epithelium Type** | **Associations** |
| 0 (1–2%) | Acinar dysplasia; fatal at birth | 0.5 cm, tracheal epithelium | – |
| I (>65%) | Macrocystic; often asymptomatic, postnatal dx | 10 cm, bronchiolar epithelium | Risk of malignancy, BAC |
| II (20%) | Small cysts; symptomatic in neonate | 2.5 cm, bronchiolar epithelium | 20% anomalies[c] |
| III (10%) | Microcystic; solid and symptomatic in neonate | 1.5 cm, bronchiolar epithelium | |
| IV (2–4%) | Newborn to 6 years; tension pneumothorax, small cysts on the periphery of lobes | 7.0 cm, distal acinar epithelium | Risk of malignancy, PPB |

BAC, bronchoalveolar carcinoma; LUL, left upper lobe; PPB, pulmonary pleuroblastoma; RML, right middle lobe.

[a]Present later with infection.

[b]Most commonly diagnosed antenatally, characterized by excess bronchiolar proliferation.

[c]Anomalies including extralobar sequestration, diaphragmatic hernia, pulmonary hypoplasia, cardiovascular malformation, hydrocephalus, skeletal malformation, jejunal atresia, Pierre-Robin syndrome, and bilateral renal agenesis/dysgenesis.

the presence and size of cysts, lung echogenicity, anatomic location, vascular supply, and associated pathophysiology including hydrops and mediastinal shift can characterize a lung lesion (see Table 4-1). Since congenital lung lesions vary in behavior from regression to causing fetal demise, the prognosis of a prenatally detected lesion is not always evident. Advances in prenatal imaging have been quintessential in defining the criteria for early therapeutic intervention in lesions adversely affecting fetal development as opposed to expectant management with postnatal resection of symptomatic cases.

A brief highlight of normal lung development is useful in conceptualizing the development of bronchopulmonary foregut malformations. The primitive foregut is the anlage of both pulmonary and gastrointestinal systems, which explains the persistent connection in some anomalies.[3] At 3 weeks, in the *embryonic* stage of gestation, lung development is initiated by the divergence of the tracheal diverticulum from the primitive foregut. Maturation of the conducting airways from the trachea to the terminal bronchioles is completed by the end of the *pseudoglandular* stage (16th week). The development of the highly differentiated respiratory unit for gas exchange occurs in the remaining 24 weeks in utero during the *cannalicular* and *terminal sac* stages wherein the distal respiratory bronchioles and alveoli are added to the pulmonary matrix. In the final 4 weeks in utero up until 8 years of age, the lung's surface area undergoes an exponential increase in alveolar growth.

## BRONCHOGENIC CYSTS

Bronchogenic cysts arise from abnormal budding of the tracheobronchial tree as true foregut anomalies to form a nonfunctioning cystic mass.[4] Two-thirds of these cysts separate early in development and thus are centrally located in the mediastinum, firmly adherent to the carina. These solitary cysts are well-encapsulated spherical lesions, lined with bronchial epithelium and mucous glands. They remain asymptomatic until superimposing infection of the fluid-filled cyst occurs: Less frequently they can be seen in a newborn due to the size of a large lesion compressing surrounding normal lung. Bronchogenic cysts should be excised to avoid further complications of infection, air trapping, and hemoptysis. Otherwise, they present as the most common benign mediastinal cyst in adulthood.

Those that appear later in development as peripheral cysts are less common and are located in the periphery of lower lobes. Since they occur during rapid bronchial division, a bronchial communication is more common. These are lined by ciliated respiratory epithelium resulting from the pseudoglandular stage of development. Respiratory distress is the most common presentation, causing cyanosis, retractions, and grunting from rapid enlargement of the cyst. Air trapping occurs during expiration due to the cyst's lack of cartilaginous support: A ball valve mechanism results in continued cyst expansion. The mass effect of the cyst causes further airway compression and distal

pulmonary hyperinflation, worsening the respiratory compromise. The cyst can be misdiagnosed as a pneumothorax, especially in the setting of a large coexistent bronchial communication; similarly a pneumothorax can be an anticipated complication.

Many of the asymptomatic lesions are discovered incidentally, or when infectious complications intervene with an air fluid level or with recurrent pneumonias localized to the same lobe, pneumothorax, hemoptysis, and upper gastrointestinal bleeding.[5-7] In congenital cystic lung lesions, 3 percent asymptomatic lesions become symptomatic within 10 months[7] and up to 10 percent can become symptomatic in 3 years.[8] Although a chest radiograph is diagnostic in over three-fourth of the cases, thin section computed tomography (CT) scanning with contrast is highly accurate in demonstrating these lesions, particularly in the setting of recurrent respiratory exacerbations.

Regardless of location and presence of symptoms, surgical resection is mandated. Resection of even asymptomatic bronchogenic cysts is advised to precede symptoms to avoid complications. Mediastinal lesions can be enucleated thoroscopically or via a thoracotomy. Segmental or lobar resection is curative for peripheral lesions.

## CONGENITAL PULMONARY ADENOMATOID MALFORMATIONS (CPAM)

CPAM, formerly known as congenital cystic adenomatoid malformations (CCAM), are hamartomatous, multicystic, or mixed adenomatoid intrapulmonary masses, arising from the overgrowth of terminal respiratory bronchioles with suppression of alveolar growth. They are usually localized to one lobe, although they can affect all lobes with equal frequency. These cystic structures may interconnect and communicate with the tracheobronchial tree.

The current classification of CPAMs[9] is a modification of the initial Stocker classification of CCAMs based on cyst size[10] to include the site of origin in the tracheobronchial tree, assuming each type correlates to a perturbation increasingly distal along the airway from trachea/bronchus to acinar/alveolar sac (see Table 4-1). Type 0 malformations are the least common, are composed of multiple, small (<0.5 cm) cysts, and are uniformly fatal at birth (see Table 4-1). Type I malformations, the "large cyst lesion," are the most common (>65%) with a typically dominant large cyst(s) (~10 cm). Type II malformations, "the small cyst lesion," occur 20 to 25 percent of the time, consist of multiple intermediate size (0.5–2.0 cm) cysts, and are associated with the highest incidence of congenital anomalies (20%), including renal dysgenesis, cardiac anomalies, congenital diaphragmatic hernia (CDH), and congenital heart disease. Type III malformations, the only one known as "the adenomatoid lesion," represent 8 percent of CPAMs and are solid appearing with tiny cysts (<1.5 cm) involving typically the entire lobe or lung. Poor prognostic indicators are often associated with Type III cysts since these microcystic lesions tend to be capable of inducing fetal hydrops and pulmonary hypoplasia. Type IV malformations are newly identified large cysts ~7 cm in size usually in one lobe that consists of nonciliated alveolar cells (Type I pneumocytes) in contrast to the ciliated cells in all other types. They often appear in newborns to 6 years of age and have an association with respiratory distress with pneumothorax or infection as well as an association with a risk of malignancy.[11-13]

Prenatally the presentation of a CPAM is highly variable with detection as early as 12 to 14 weeks. For an attempt at a more clinically relevant classification, the ultrasonographic appearance was used as the basis by Adzick et al. using either macrocystic with cysts >5 cm (previously Type I) or microcystic with cysts <5 cm (Type II or III depending on the underlying histology).[14] Macrocystic has a more favorable prognosis and microcystic is more solid with an unfavorable prognosis associated with more anomalies. What has more recently become evident is the recognition of "hybrid" lesions containing features of both CPAMs and bronchopulmonary sequestrations (BPS) indistinguishable until histologic review. Thus, the differential diagnosis of a prenatal cyst can include a variety of lesions, such as CPAM, bronchopulmonary sequestrations, bronchogenic cyst, congenital lobar emphysema (CLE), esophageal duplication cyst, and a CDH (see Fig. 4-1). Thus, further imaging with Doppler ultrasonography can detect the anomalous blood supply to the aorta found with sequestrations. CT imaging can correlate with a pathologic diagnosis of a CPAM with 100 percent concordance.[15] Magnetic resonance imaging (MRI)/fetal MRI can assist in distinguishing whether an echogeneic lung mass is a Type III CPAM or a CDH given the heterogeneity of the mass.

The natural history of these lesions is unpredictable and can range from complete regression in 25 percent to 20 percent that are symptomatic prenatally, and then the ~5 percent category of those with such a rapid growth that mediastinal shift, caval obstruction, impaired cardiac filling, and subsequent nonimmune hydrops and polyhydramnios result.[16] CPAMs without hydrops have a generally favorable survival rate, whereas those 5 percent of CPAMs that develop hydrops and anasarca are associated with a higher mortality rate of up to 100 percent without intervention.[17,18] Large masses causing fetal hydrops in a fetus <32 weeks require in utero intervention to reverse the hydrops and potential fetal demise.[19] In macrocystic lesions, cyst aspiration and thoracoamniotic shunting have been used to alleviate mediastinal compression and hydrops. In contrast, in microcystic lesions, open fetal surgery has been a surgical option to treat those lesions causing hydrops fetalis. CPAMs may grow progressively or regress by unclear mechanisms. Maternal administration of betamethasone has been associated with resolution of hydrops and an increased survival in fetuses with high-risk CPAMs compared with historical controls[20,21]: These findings may be related to a reduction in CPAM growth or improved maturation and need to be

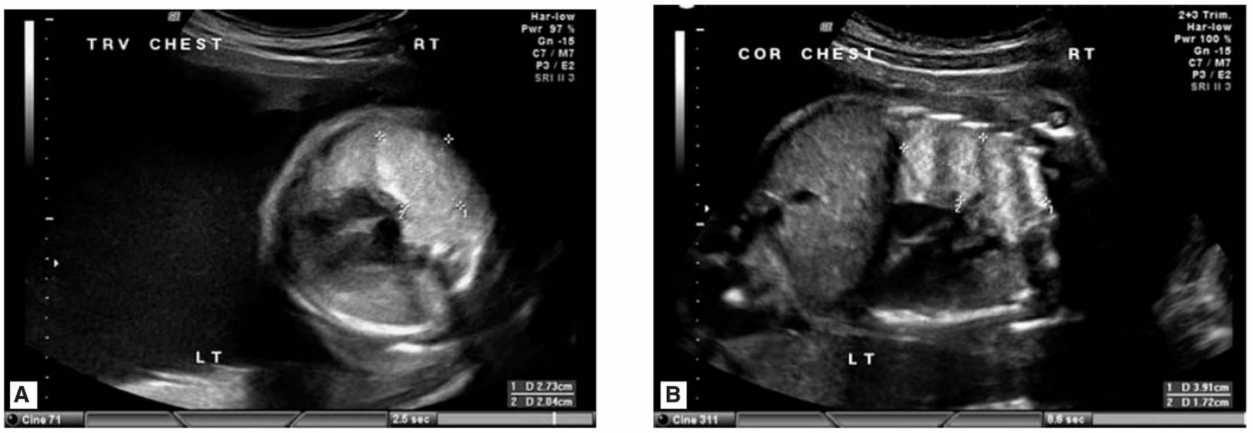



**FIGURE 4-1** Ultrasound of thoracic mass: **A.** Transverse view and **B.** coronal view. This CPAM was demonstrated at 18 weeks filling the thoracic cavity and resolved by 35 weeks of gestation.

confirmed in a controlled trial as opposed to being compared to historical controls.[22]

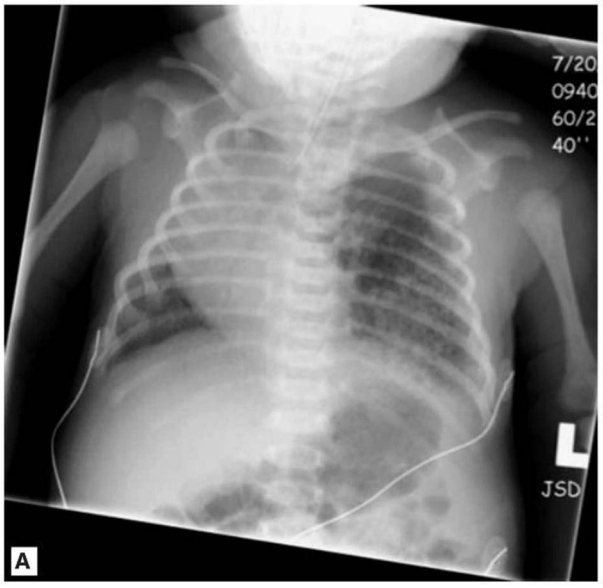
Of those who are symptomatic postnatally, 80 percent present with respiratory distress compared to 20 percent who present more subtly with recurrent infections. Symptoms at birth are often due to the mass effect causing mediastinal shift, pneumothorax, or pulmonary hypoplasia.[14,23] The size of the lesion dictates the degree of respiratory distress. Large cysts can produce respiratory distress with such expansion of the cysts from air trapping that the contralateral lung is compressed. Microcystic lesions are also more frequently associated with distress in the newborn period. A radiograph or CT can demonstrate the hyperexpanded lung with contralateral herniation and mediastinal shift (see Fig. 4-2). Those who are symptomatic, with respiratory distress, recurrent infections, or a pneumothorax, require surgical resection and the urgency of resection depends on the symptoms. The majority of children (>60%) remain asymptomatic postnatally[23] and the management remains controversial since the potential to become infected, cause hemoptysis, pneumothorax, or hemothorax, or undergo malignant degeneration persists. At least 8 percent of congenital lung lesions spontaneously regress by 9 months, so the timing of surgery can wait for that period of potential resolution.[24] In a large series, 3 percent of asymptomatic lesions can become symptomatic in that time frame.[8] All lung lesions, even disappearing lung lesions, prenatally need to be reconfirmed by postnatal imaging since CT scans can best identify a detectable malformation unvisualized on plain chest x-ray (CXR)[25] (see Fig. 4-3).

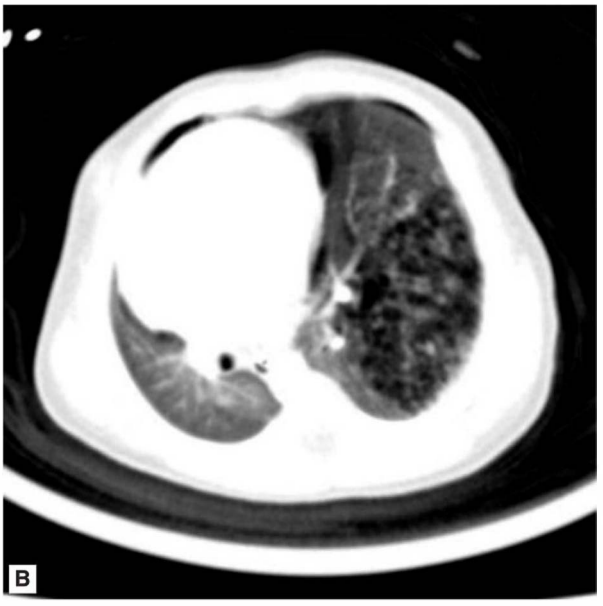
There is a rare association of CPAMs with malignancies, and 8.6 percent of malignant tumors have been shown to be associated with prior cystic malformations,[13] such as bronchioalveolar carcinoma (BAC) in older children and adults, pleuropulmonary blastomas (PPB) in young children, and embryonal rhabdomyosarcomas. PPB are the most common malignancy associated with early childhood cysts (Type IV) with 0.35 to 0.65 PPB cases per 100,000 births.[2] Later in childhood, BAC occurs and can be associated with Type I cysts, and cystic synovial sarcoma appears de novo. Despite the confusion in the literature, PPB is not a premalignant CPAM, since cytogenetic abnormalities (Trisomy 8) are distinctly found in PPB suggesting that the earliest presentation of a low-grade cystic malignancy that can convert into a sarcomatous disease over 12 to 72 months.[26,27] Malignancies have been reported later even after resection of the CPAM. So not only does elective resection for pathologic certainty require close surveillance postresection, but also prophylactic resection of a lung cyst will not prevent the later development of PPB.[28]

Definitive therapy is surgical resection. An elective anatomic lobectomy, either via an open or a thoracoscopic approach, remains the procedure of choice to avoid incomplete resection, persistent pneumothorax, and potential recurrence. Multilobar involvement is best treated by a lobectomy with a segmental resection for a parenchymal-sparing procedure.[29] Postoperatively, respiratory compromise may acutely worsen in neonates with coincident pulmonary hypoplasia and pulmonary hypertension, requiring extracorporeal membrane oxygenation.

## PULMONARY SEQUESTRATION

A pulmonary sequestration is an ectopic mass of nonfunctioning lung tissue with an anomalous systemic artery and without a bronchial connection to the tracheobronchial tree. Sequestrations are classified as either intralobar or extralobar.[4,30] The majority are intralobar, as an anomalous intraparenchymal lesion without investing pleura. Extralobar sequestrations are separate from the normal lobe and contained within a distinct visceral pleura. The typical blood supply is from the systemic circulation arising from the descending or abdominal aorta (75%) or other thoracic vessels (25%): This systemic blood supply is characteristically



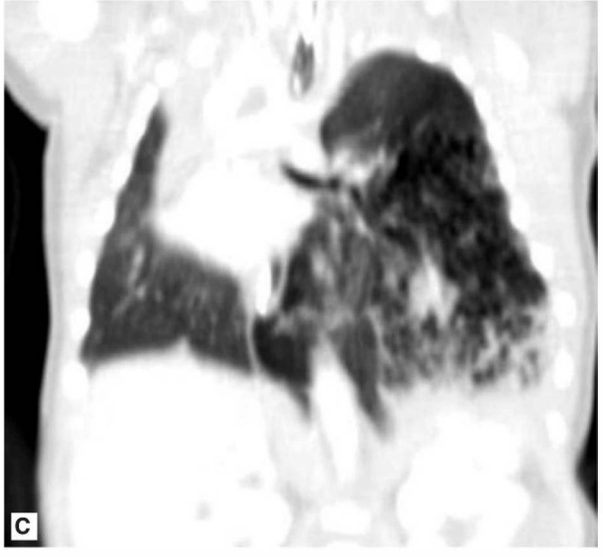




**FIGURE 4-2** **A.** CXR of left CPAM in a newborn in respiratory distress. **B.** Thoracic CT of left CPAM in newborn (sagittal cuts). **C.** Thoracic CT with coronal reconstructions of thoracic mass in newborn—left lower lobe identified. Note mediastinal shift and apparent compression of left upper lobe consistent with presentation of respiratory distress. (CPAM, congenital pulmonary airway malformation; CLE, congenital lobar emphysema).

identified upon imaging. The systemic feeding arteries often are multiple and branch off the aorta, and up to 15 percent are infradiaphragmatic. Multiple theories attempt to postulate the derivation of sequestrations, assumed to develop as accessory lung buds off an anomalous aortic branch that separates due to traction upon further growth.

Most sequestrations are in the left lower lobes. The most common type is the "Rokitansky lobe," which occurs on the left with a feeding vessel from the aorta. However, 15 percent of sequestrations are located below the diaphragm as a retroperitoneal mass, called an "abdominal accessory lobe."[31] Sequestrations often have a patent communication with the gastrointestinal tract, and extralobar types are associated with congenital anomalies (50–65%) such as congenital diaphragmatic hernia,[31] bronchial atresia, colonic duplication, pulmonary hypoplasia, absent pulmonary artery, vertebral anomalies, and esophageal communication.[4,32] Because of the associated diaphragmatic defects, radioisotope scanning of right lower lobe lesions can distinguish a herniated liver from a right lower lobe sequestration.

Typically the extralobar sequestration is asymptomatic and found incidentally prenatally or due to the associated congenital anomalies. Despite no connection to the tracheobronchial tree, the sequestration may become infected by hematogenous spread causing respiratory distress from recurrent pneumonia. Symptoms may also reflect the

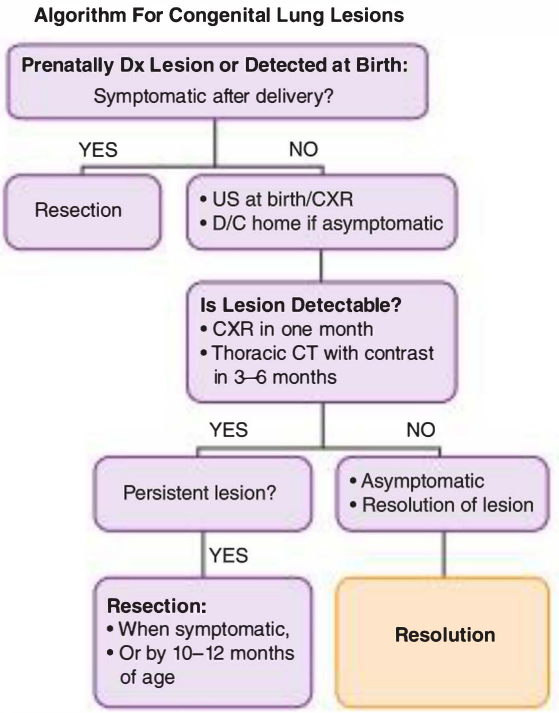



**FIGURE 4-3** Algorithm for congenital lung lesions.

secondary cardiac manifestations from the coincident large venous shunts to the systemic circulation. Typical venous drainage is to the systemic circulation (inferior vena cava, azygous vein, or portal vein) creating a left-to-right shunt; thus, large shunts are at risk for potentially creating high-output cardiac failure. The scimitar syndrome is due to anomalous venous return to the vena cava creating a left-to-right shunt, and the venous drainage appears as a sickle-shaped shadow in the right lower lobe.[31]

Intralobar lesions remain asymptomatic until recurrent infections or hemoptysis occurs. A cystic or atelectatic mass is present on plain radiographs but definitive diagnosis requires documenting a systemic arterial supply by Doppler ultrasonography or nuclear magnetic resonance angiography: Both techniques are more frequently used than angiography, the prior gold standard. All sequestrations should be excised to avoid future complications with infection and fatal hemoptysis. Intralobar lesions may require a lobectomy, and extrapulmonary lesions require an excision that can be accomplished by standard thoracotomy or more recently by thoracoscopic resection.[33,34]

## CONGENITAL LOBAR EMPHYSEMA

CLE is a rare cause of respiratory distress in the newborn and is characterized by overexpansion of a pulmonary lobe and alveolar overdistension. A variant of bronchomalacia can cause CLE with focal cartilaginous deficiency of the tracheobronchial tree, resulting in regional airway collapse with expiration and then air trapping leading to emphysematous changes. Over one-half are diagnosed by 1 month of age and presentation after 6 months is unusual. A chest radiograph is sufficient to diagnose a large emphysematous lobe with atelectasis in the ipsilateral lobe. The upper lobes are most commonly involved with the following incidence—left upper lobe (42%), right middle lobe (35%), right upper lobe (21%), and bilaterally (20%).[30] The etiology is not clear in the majority of cases; however, both bronchial cartilaginous dysplasia and polyalveolar lobes are the pathologies present in a quarter of cases each. Extrinsic compression can occur from an intrathoracic mass such as a vascular or cardiac anomaly, teratoma, vascular ring, or patent ductus arteriosus. Even the end stage of respiratory distress syndrome in a neonate with chronic pulmonary interstitial emphysema (PIE) can evolve into CLE. Alveolar cells make up the emphysematous tissue seen in both CLE and CPAM Type IV that are pathologically similar. Twenty percent of associated malformations are cardiac anomalies (PDA, ventricular septal defect [VSD], and tetralogy of Fallot). Moderate distress presents initially until the lobe gradually enlarges causing cyanosis by continued compression of the uninvolved lung due to continued expansion. Severe life-threatening distress is rare but may require immediate surgical intervention, a thoracotomy, to allow the overinflated lobe to decompress upon herniation and to prevent the intrathoracic compression by a lobectomy. Bronchoscopy and positive pressure ventilation can exacerbate the underlying pathophysiology of CLE creating a life-threatening situation, which can only be relieved by rapid thoracotomy to decompress the hyperventilated lobe. Many lesions can resolve spontaneously but surgical intervention, a lobectomy, is indicated in those lesions that are symptomatic from compression of the normal lung and mediastinum.[35]

These varied congenital lung malformations are relatively unusual individually. Early diagnosis requires a high index of suspicion and familiarity with their presentation since they are difficult to detect. Whereas early diagnosis is amenable to an uncomplicated surgical resection, a delay in diagnosis can be associated with substantial morbidity.

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## CONGENITAL PULMONARY DISORDERS BOARD REVIEW QUESTIONS (CHAPTER 4)

1. Which of the following is correct regarding bronchogenic cysts?
   A. One-third of cysts develop early and are centrally located.
   B. Bronchogenic cysts are usually spherical and lined with intestinal epithelium.
   C. Thirty percent of clinically silent cysts will become symptomatic within 10 months of age.
   D. Segmental resection is appropriate for peripheral lesions.
   E. Up to 25 percent of congenital cysts will spontaneously regress by 9 months of age.

2. Which is correct regarding congenital pulmonary adenomatoid malformation (CPAM)?
   A. This lesion is a result of terminal respiratory bronchiole undergrowth.
   B. It is usually localized to one lobe.
   C. Type 0 malformations are the most common.
   D. Type 1 malformations are associated with the highest incidence of congenital anomalies.
   E. Type 3 malformations are generally larger than 7 cm.

3. Which is true for congenital pulmonary adenomatoid malformation (CPAM)?
   A. CPAM may grow or regress by unclear mechanisms.
   B. Twenty percent present with respiratory distress.
   C. Microcystic lesions are less frequently associated with respiratory distress.
   D. CPAM is classified as a premalignant pleuropulmonary blastoma.
   E. Thoracoscopic wedge resection is the preferred surgical option.

4. Which is true regarding pulmonary sequestration?
   A. The majority are extralobar.
   B. Up to 75 percent of systemic feeding arteries are infradiaphragmatic.
   C. Most sequestrations occur in the left lower lobe.
   D. Sequestrations rarely have a patent communication with the gastrointestinal tract.
   E. The intralobar form is associated with congenital anomalies in 40 percent of patients.

5. Which is true regarding congenital lobar emphysema (CLE)?
   A. It is characterized by underexpansion of a lobe due to alveolar underdistension.
   B. Presentation after 6 months is unusual.
   C. The most commonly involved lobe is the right upper lobe.
   D. Fifty percent of associated anomalies are cardiac.
   E. Bronchoscopy and positive pressure ventilation is the treatment of choice.

## ANSWERS

1. **Answer: D.** Segmentectomy or lobectomy is appropriate therapy for peripheral cysts. Two-thirds of cysts develop early and are centrally located. Bronchogenic cysts are usually spherical and lined with bronchial epithelium. Only 3 percent of clinically silent cysts will become symptomatic within 10 months of age. Up to 8 percent of cysts will spontaneously regress by age 9 months.
2. **Answer: B.** CPAM is usually localized to one lobe. It is the result of terminal respiratory bronchiole overgrowth. Type 1 malformations are the most common. Type 2 malformations have the highest association with congenital anomalies. Type 3 malformations have multiple cysts <1.5 cm.
3. **Answer: A.** CPAM may grow or regress spontaneously by unclear mechanisms. Eighty percent present with respiratory distress, which most frequently is associated with microcystic lesions in the newborn. CPAM is not a premalignant lesion. Anatomic lobectomy is the procedure of choice.
4. **Answer: C.** Most sequestrations occur in the left lower lobe. The majority are intralobar and often have a patent communication with the gastrointestinal tract. About 15 percent of systemic feeding arteries arise below the diaphragm. The extralobar form is associated with congenital anomalies in 40 percent of cases.
5. **Answer: B.** Presentation is most common during the first month of life. CLE is characterized by alveolar overdistension with subsequent overexpansion of the lobe. The most commonly involved lobe is the left upper lobe. Twenty percent of associated anomalies are cardiac. Bronchoscopy and positive pressure ventilation can worsen the pathophysiology and create a life-threatening situation.

# 5 Benign Diffuse Pulmonary Disorders

*Christian A. Merlo*

**KEY CONCEPTS**

- Epidemiology
  - Diffuse benign pulmonary disorders cover a broad range of primary lung diseases and can be associated with systemic disorders.
- Pathophysiology
  - Most benign pulmonary disorders are derived from intrinsic or extrinsic injury. Such injury can take the form of cellular and/or humoral immunologic injury triggered by inhaled antigens, infectious agents, or autoimmune processes. Chemical injury from smoking or certain drugs has also been implicated.
- Clinical features
  - Most presenting symptoms include progressive dyspnea and cough. Other symptoms include chest pain, wheezing, and hemoptysis. Physical signs include heavy use of accessory muscles of breathing, cyanosis, and clubbing. Systemic signs of illness seen with some illnesses include fatigue, weight loss, and malaise.
- Diagnostics
  - Most diffuse benign disorders are characterized by plain chest radiography, computed tomography, and open or video-assisted thoracoscopic lung biopsy. Most of these disorders have characteristic radiologic pulmonary parenchymal patterns, adenopathy (e.g., sarcoidosis), and histologic characteristics. Bronchoscopy with transbronchial biopsies/bronchoalveolar lavage, fine-needle aspiration biopsies, and sputum cultures and/or cytologies is also helpful in many cases. Finally, a complete blood count with differential (e.g., eosinophilic processes) and serum chemistries are helpful in some cases.
- Treatment
  - Although treatment recommendations vary with the particular pulmonary process, many are corticosteroid based while others are predicated on removal of an inciting agent (e.g., drug, tobacco smoke).
- Outcomes
  - Clinical outcomes vary widely according to the particular process.

## INTRODUCTION

Diffuse benign pulmonary disorders cover a broad range of primary lung diseases but may also be associated with systemic disorders. These range from chronic conditions such as idiopathic pulmonary fibrosis (IPF) associated with poor survival to acute disease of hypersensitivity pneumonitis (HP) with usually a good response to treatment. Some of these diseases have unique clinical characteristics while others share similar radiographic changes, symptoms, or pulmonary function abnormalities. Therapy differs for many of the diffuse benign pulmonary diseases, making accurate diagnosis paramount.

Each of these disorders may occur due to intrinsic or extrinsic injury. For instance, the pneumoconioses are due to the inhalation of damaging foreign material into the lung, while HP is due to an allergic response to foreign material or medications. On the other hand, interstitial lung diseases such as IPF, sarcoidosis, lymphangioleiomyomatosis (LAM), eosinophilic granulomatosis (EG), and the pulmonary disorders associated with collagen vascular disease are believed to be due to intrinsic lung inflammation and injury.

The benign diffuse lung diseases may also be categorized based on physiologic presentation, particularly the type of change seen by pulmonary function studies. Some of the disorders are associated with an obstructive ventilatory defect (LAM, EG) or restrictive ventilatory defect [IPF, nonspecific interstitial pneumonitis (NSIP), asbestosis], while others may present with combined obstruction and restriction

[sarcoid, bronchiolitis obliterans with organizing pneumonia (BOOP)].

Finally, these diseases may be categorized based on radiographic findings (i.e., diffuse interstitial infiltrates, alveolar infiltrates, cystic lesions, or honeycombing). This chapter reviews the most common benign pulmonary diseases including clinical presentation, diagnosis, and treatment.

## IDIOPATHIC PULMONARY FIBROSIS (IPF)/USUAL INTERSTITIAL PNEUMONITIS (UIP)

IPF is a progressive, fatal disease with no known cause. It is manifest by diffuse interstitial lung scarring with a predominance of fibrosis in the subpleural and lower lung zones.[1] This disease has several different names, including cryptogenic fibrosing alveolitis, usual interstitial pneumonitis, and IPF. IPF is progressive, refractory to therapy, and ultimately leads to respiratory compromise and death, usually within 5 years of diagnosis.[2–5] The typical patient presents in the seventh decade of life with gradual onset of shortness of breath and a dry, nonproductive cough. Young patients can be affected, however, particularly in familial forms of the disease. IPF is frequently misdiagnosed as "pneumonia" because common symptoms of cough and dyspnea are associated with pulmonary infiltrates; however, the protracted course and lack of fever and purulent sputum make pneumonia less likely. Physical examination typically demonstrates bilateral "Velcro-like" crackles, predominantly in the lung bases. Resting or exercise-induced hypoxemia is often present. Chest radiographs show small lung volumes with interstitial infiltrates predominantly in the lower and peripheral lung zones (Fig. 5-1). High-resolution computed tomography (HRCT) of the chest can help distinguish the diagnosis of IPF from other interstitial lung disorders. Typical findings include peripheral and lower lung zone interstitial thickening with honeycombing and traction bronchiectasis[6,7] (Fig. 5-2A and B). The fibrosis and honeycombing may be interspersed with relatively normal-appearing lung parenchyma. Pulmonary function studies show a restrictive ventilatory defect with a low diffusing capacity for carbon monoxide (DLCO).[7] As the disease progresses, the total lung capacity, vital capacity, and DLCO fall, indicating worsening fibrosis. In the early stages of the disease, oxygen desaturation may occur only with exercise; but as the disease progresses, severe resting hypoxemia is a common finding.[7]



**FIGURE 5-1** PA chest x-ray of a patient with IPF. Note small lung volumes and lower lobe interstitial infiltrates.

The diagnosis of IPF is established by open lung biopsy together with appropriate clinical and radiographic findings.[1,7] Transbronchial bronchoscopic biopsies are frequently performed by many practitioners for interstitial lung disease and may be useful to exclude other diagnoses such as

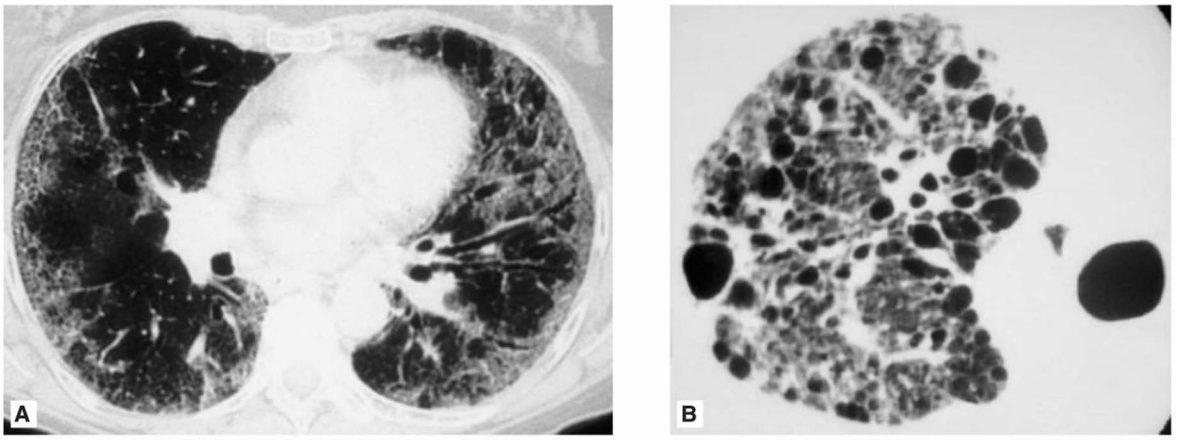



**FIGURE 5-2** **A.** High-resolution chest CT of IPF showing peripheral interstitial fibrotic infiltrates with areas of traction bronchiectasis interspersed with areas of normal lung parenchyma. (Courtesy of Stanley Siegelman, MD.) **B.** Close-up view of HRCT showing marked honeycombing and interstitial fibrotic changes in a patient with IPF.

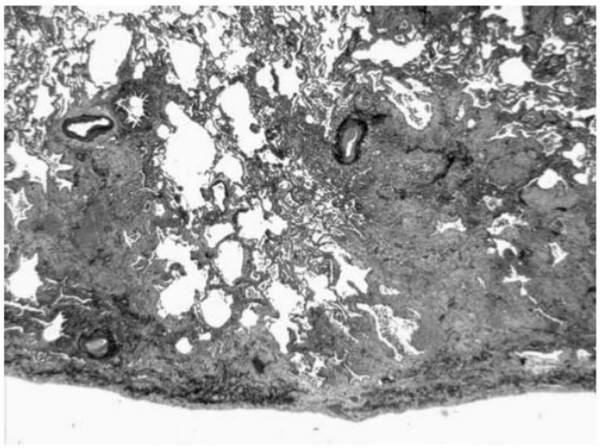


**FIGURE 5-3** Histologic appearance of IPF from an open lung biopsy. Note areas of honeycombing with interstitial thickening and fibrosis.

sarcoidosis, BOOP, eosinophilic pneumonia, or extrinsic allergic alveolitis. However, transbronchial biopsies are inadequate to establish the diagnosis of IPF because a larger tissue sample is necessary to visualize the geographic changes seen in this condition. These include areas of fibrosis and honeycombing interposed between areas of normal-appearing lung[1,7] (Fig. 5-3). Thus, video-assisted thoracic surgical (VATS) biopsy has become the standard approach if a tissue diagnosis is warranted. It is important to note that there is controversy regarding the need to establish a tissue diagnosis when all clinical and radiographic findings suggest the diagnosis of IPF.[8] This is particularly true for older patients and those with far advanced disease. For those patients who are younger with atypical findings, open biopsy should be considered.

There is no known effective medical treatment for IPF. High-dose corticosteroids (1 mg/kg methylprednisolone) given for several weeks and followed by a gradual taper has been the mainstay of therapy for many years, with few patients improving.[7] One study showed minimal improvement with a combination of prednisone and azathioprine,[9] but widespread success with this approach has not been reported. Other potent agents such as cyclophosphamide have been used, also with limited success.[7] Gamma interferon has also been studied but has little clinical benefit.[10,11] For patients below 65 years of age who are otherwise healthy, lung transplantation remains the only viable treatment option for IPF.

## NONSPECIFIC INTERSTITIAL PNEUMONITIS

After Liebow and Carrington proposed the first major classification scheme for the idiopathic interstitial pneumonias (IIP),[12] several investigators found that a significant number of biopsies did not fit into the described subtypes.[13,14] The term *nonspecific interstitial pneumonitis* (NSIP), first used by Katzenstein, represents a distinct histologic type of interstitial *pneumonitis* with clinical characteristics that differ from UIP/IPF.

Although NSIP and IPF may be clinically indistinguishable, there are some differences that may help to differentiate these two diagnoses. Patients with NSIP typically present with subacute symptoms rather than the insidious onset characteristic of IPF.[15] Fever is also a common complaint among patients with NSIP and is rare in IPF.

Radiographically, NSIP typically has diffuse bilateral ground-glass opacities on HRCT.[16] Honeycombing is a hallmark feature of IPF but is not present in NSIP. Alveolar infiltrates and occasionally nodules have been described in NSIP, but these are not common.

The diagnosis of NSIP is made by open or VATS lung biopsy (Fig. 5-4). Katzenstein originally divided biopsies among three groups based on the amount of fibrosis present.[14] Group I consisted of interstitial infiltrates with predominant lymphocytes, occasional plasma cells, and minimal fibrosis. The infiltrates were noted to be temporally uniform, in contrast to the lesion of UIP, which is temporally heterogeneous. Group II contained the interstitial infiltrates but had marked amounts of associated fibrosis. Group III included marked distortion of the lung architecture from collagen deposition, scarring, and occasional honeycombing.

The prognosis for NSIP is much better than that for IPF. The majority of patients will improve or recover (74% in one series).[15] However, the likelihood of improvement depends on the severity of fibrosis. Patients with Katzenstein Group III NSIP (severe fibrosis) have the least favorable prognosis. Corticosteroids with or without other immunosuppressive agents are the mainstay of therapy. However, it is important to note that there are no randomized controlled trials proving benefit for any form of therapy, and a number of patients have improved without specific treatment.

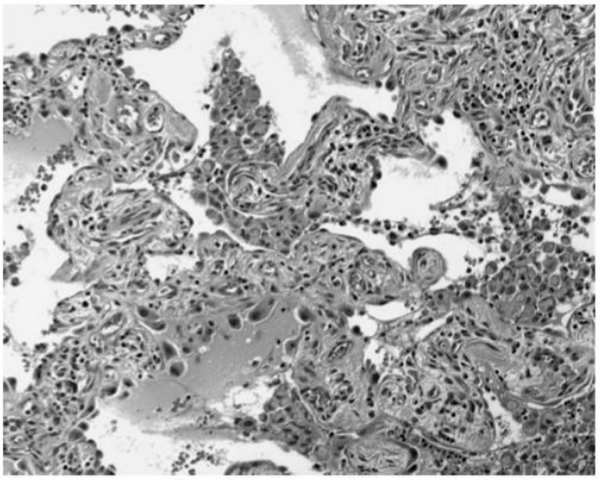


**FIGURE 5-4** Open lung biopsy specimen from a patient with nonspecific interstitial pneumonitis showing diffuse interstitial thickening with inflammatory cells and collagen. (Courtesy of Rubin Tuder, MD.)

## CRYPTOGENIC ORGANIZING PNEUMONIA/BRONCHIOLITIS OBLITERANS ORGANIZING PNEUMONIA

First described in 1983[17] and then again in 1985[18] under the name BOOP, cryptogenic organizing pneumonia (COP) is an increasingly recognized cause of pulmonary disease. Disagreement continues to exist regarding the name for this process; thus, both names are used interchangeably.[19] Although the term BOOP is more commonly used in the United States, COP is preferred, as designated by the American Thoracic Society and European Respiratory Society. COP specifically refers to the idiopathic form of the disease. However, organizing pneumonia, the histologic correlate, has been identified in association with a variety of diseases as well as drug and inhalational exposures.

COP can present in a variety of forms.[20–23] The most common is a nonresolving pneumonia.[18,20–23] Patients typically complain of fevers, cough, and malaise. Myalgias have been described in a number of patients. Symptoms usually are present for several months, and patients may have been treated with one or multiple courses of antibiotics without significant improvement. Inspiratory squeaks are often present on physical examination.

Mild leukocytosis is common, as well as an elevated erythrocyte sedimentation rate, which may sometimes be over 100. Pulmonary function testing can show a combination of restriction and obstruction as well as a reduced diffusion capacity. Frank hypoxemia is rare.[18]

Chest radiography typically shows multiple areas of patchy alveolar infiltrates bilaterally.[18] CT scans most commonly show areas of consolidation with air bronchograms; however, a variety of other patterns have also been described (Fig. 5-5).[18,21] These range from a diffuse nodular pattern to band-like areas of consolidation. Pleural effusions are uncommon.

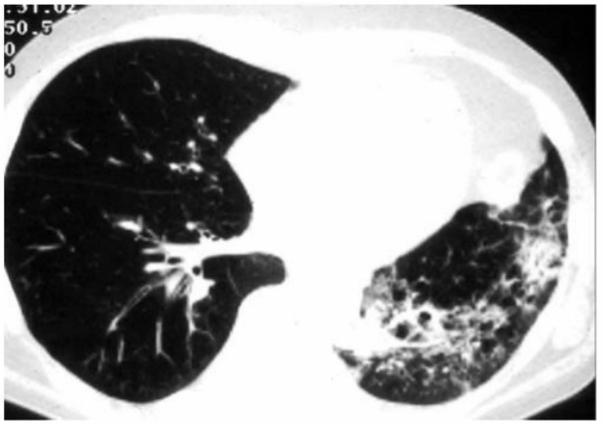


**FIGURE 5-5** Chest CT scan showing the patchy infiltrates characteristic of BOOP.

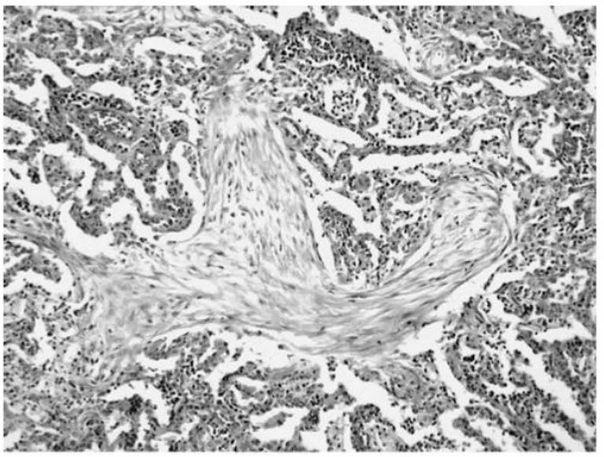


**FIGURE 5-6** Histopathologic specimen from a patient with BOOP. Note tufts of loose collagen plugging the airway.

The diagnosis of COP is made by lung biopsy, which shows the histologic features of organizing pneumonia (Fig. 5-6).[18,20–24] Although transbronchial biopsies are mostly sufficient, the small biopsies obtained by this procedure may be insufficient to completely distinguish the process from other underlying pathology.[19,23,24] It is important to exclude other processes, since organizing pneumonia can sometimes be found in association with other entities, such as fibrotic disease. VATS or open lung biopsy may be necessary in some circumstances to establish a firm diagnosis.

Treatment consists of glucocorticoids for 6 to 12 months.[18,20–24] Patients typically have a good response, with close to two-thirds having clinical remission within a short time. However, relapses while tapering steroids are common. Relapses typically respond to reinstitution of higher doses of glucocorticoids and do not appear to affect the long-term course of the disease.

COP has had other notable presentations.[18,20–24] Focal lesions resembling solitary lung nodules have been described by a number of authors. The diagnosis was typically found after surgical resection, which stemmed from the concern that the nodules were a malignant process. The patients tended to do well without any further treatment. A rapidly progressive form of COP has also been described.[25] This form advances much more rapidly, with a fulminant course and high mortality.

## OTHER IDIOPATHIC INTERSTITIAL PNEUMONIAS

IPF, NSIP, and COP make up the majority of the IIP encountered in clinical practice. There are other forms of IIP that are less common and are dealt with briefly below.

### Acute Interstitial Pneumonia (AIP)

AIP is a rapidly progressive interstitial disease with typically a fulminant course.[19] It typically presents with a viral-like prodrome of myalgias, fever, chills, and malaise. Patients usually present within 3 weeks of onset of the illness and most require mechanical ventilation. CT reveals diffuse ground-glass opacification and, to a lesser extent, basilar airspace consolidation. The histologic lesion is that of diffuse alveolar damage. Mortality is high, well over 50 percent, and there is no effective therapy.

### Respiratory Bronchiolitis-Associated Interstitial Lung Disease (RB-ILD) and Desquamative Interstitial Pneumonia (DIP)

Respiratory bronchiolitis is a pathologic lesion found in cigarette smokers; it is characterized by pigmented macrophages in the lumens of the first- and second-order respiratory bronchioles.[19] These lesions are most often seen incidentally on biopsies done for unrelated reasons and rarely cause symptoms. However, a small percentage of patients do present with clinically significant interstitial disease with this lesion on biopsy; the clinical condition is then termed RB-ILD.

The clinical spectrum ranges from minimal complaints to severe dyspnea.[19] The most common symptoms are gradually progressive dyspnea and new or worsening cough. Males are more likely to be affected than females. CT typically reveals centrilobular nodules, thickened airways, and sometimes ground-glass opacification. Patients almost universally improve with cessation of smoking.

The pathologic lesion of DIP is an accumulation of macrophages in the alveolar spaces.[19] Because of its similar male predominance, association with cigarette smoking, and the presence of macrophages, DIP is thought to represent one end of a spectrum of disease, where the other end would be RB-ILD. However, there are some differences, such as the uniform presence of ground-glass opacification seen in DIP. Honeycombing can be seen in DIP, but only in a minority of patients, and it tends to be very limited in extent. As with RB-ILD, the prognosis is good, with smoking cessation thought to be important. Patients with DIP are commonly treated with corticosteroids, but there have been no treatment trials proving benefit.

### Lymphoid Interstitial Pneumonia (LIP)

LIP is the last of the IIP included in the recent consensus classification.[19] This disease is most often seen in combination with other diseases such as Sjögren syndrome, acquired immunodeficiency syndrome, various autoimmune diseases, and Castleman disease.[19,26,27] The disease tends to affect women more than men. Initial presentations include slowly progressive shortness of breath, cough, and weight loss. CT typically reveals a pattern of bilateral diffuse or patchy ground-glass opacification, with poorly defined centrilobular nodules.[27] Thickening of the peribronchiovascular bundles and irregular septal thickening are also common.[27] Cystic changes are noted in a majority of patients, but honeycombing is less common.

The histology of LIP is marked by a dense infiltration with lymphocytes and plasma cells.[19,26] The infiltration is especially marked in the alveolar septum. Lymphoid follicles and germinal centers are commonly seen.

The prognosis is highly variable, with the majority of patients remaining stable or improving; however, over one-third of patients may have progressive disease.[19,26,27] Treatment usually consists of corticosteroids with or without other immunosuppressive agents.

## INTERSTITIAL LUNG DISEASE ASSOCIATED WITH COLLAGEN VASCULAR DISEASE

The collagen vascular diseases present with a wide range of symptoms and findings, and they have variable courses. Given the systemic nature of the diseases, it is not unexpected to find that patients commonly develop pulmonary pathology. The full range of known complications is beyond the scope of this chapter and have been described in detail elsewhere.[28] The complications are not limited to the lung parenchyma but rather include all aspects of the respiratory system as well as the respiratory muscles, pleural space, upper airway, and pulmonary vasculature. The complications also do not always represent a direct injury caused by the underlying collagen vascular disease. Some of the therapies for these diseases have pulmonary side effects, such as methotrexate-induced lung injury in patients being treated for rheumatoid arthritis or pulmonary infections from immunosuppression. Bibasilar fibrosis from repeated aspirations due to esophageal dysmotility from scleroderma has been well described.

Histologically, the types of interstitial disease found include those that have been previously mentioned. These comprise nonspecific interstitial pneumonia, UIP, and BOOP.[28,29] Other forms of interstitial disease have also been described, including lymphocytic interstitial pneumonia and diffuse alveolar damage.[28,29] Prognosis depends on the histologic type of interstitial disease and is largely similar to that seen in patients without underlying collagen vascular disease.

## SARCOIDOSIS

Sarcoidosis is a multiorgan disease with almost all cases having pulmonary manifestations at some point during its course.[30] Pulmonary manifestations range from asymptomatic hilar adenopathy, to endobronchial involvement with airflow limitation to diffuse nodules to end-stage lung fibrosis.

Sarcoidosis has a worldwide distribution and affects different racial and ethnic groups variably. In the United States, annual incidence estimates are 10.9 cases per 100,000 Whites and 35.5 cases per 100,000 Blacks.[31] The etiology remains unknown, but some epidemiologic research supports an infectious etiology whereas other evidence suggests an environmental exposure.[30]

The clinical presentation of pulmonary sarcoidosis is highly variable. Probably the most common is asymptomatic hilar adenopathy found on chest radiography done for an unrelated reason.[30,32] Common pulmonary symptoms include cough, dyspnea, and retrosternal chest pain. Systemic symptoms include fatigue, weight loss, and malaise.[30,32] Löfgren syndrome is a notable acute presentation of sarcoidosis characterized by the triad of hilar lymphadenopathy, polyarthralgias, and erythema nodosum.

Sarcoidosis is staged by chest radiograph.[33] Stage I disease is defined as the presence of hilar lymphadenopathy without other parenchymal infiltrates (Fig. 5-7), whereas stage II includes hilar lymphadenopathy with infiltrates. In stage III disease, there are infiltrates without hilar lymphadenopathy, and stage IV disease is defined by the presence of end-stage fibrosis (Fig. 5-8). Classically, sarcoidosis affects the upper and midlung zones. Small nodules ranging in size from 2 mm to 1 cm in diameter are the most common finding.[33] The nodules are typically found around the bronchovascular bundles. Patchy areas of airspace consolidation can also be seen, leading to the term *alveolar sarcoidosis*.[33] Mediastinal adenopathy is very common on CT, with calcification present in approximately 50 percent of patients, typically in a focal or "eggshell" pattern.[33]



**FIGURE 5-7** Chest x-ray showing bilateral hilar adenopathy without pulmonary infiltrates, depicting stage I pulmonary sarcoidosis.

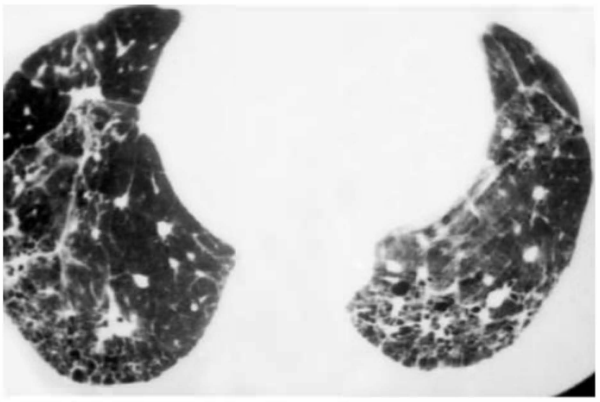


**FIGURE 5-8** Bilateral fibrotic changes as seen in stage IV pulmonary sarcoidosis.

Histologically, the lesion of sarcoidosis is the noncaseating granuloma. Granulomas are tightly packed and composed of epithelioid cells, including multinucleated giant cells and lymphocytes[30–32,34] (Fig. 5-9). These lesions can be found in lymph nodes, the lung parenchyma, and airway mucosa. However, noncaseating granulomas are not unique to sarcoidosis and other etiologies must be excluded clinically and pathologically, including fungal and mycobacterial disease, HP, pneumoconiosis such as beryllium-induced lung disease, and drug reactions.[34]

No treatment is needed for asymptomatic patients with hilar adenopathy. The majority of these patients and patients with Löfgren syndrome will have complete spontaneous remissions.[32] Corticosteroids are the mainstay of treatment for symptomatic sarcoidosis. Other immunosuppressive

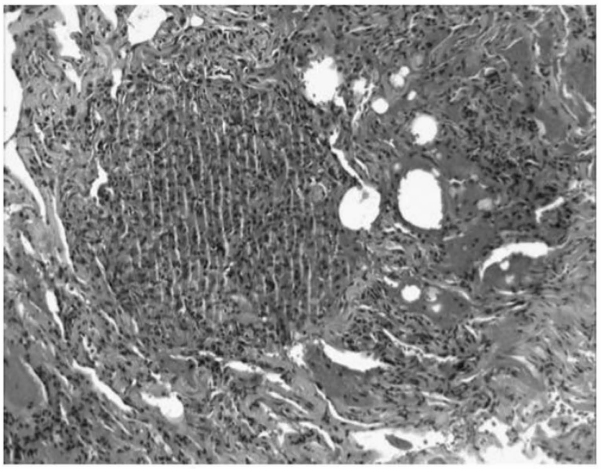


**FIGURE 5-9** Transbronchial lung biopsy showing typical noncaseating granuloma from a patient with pulmonary sarcoidosis. (Courtesy of Rubin Tuder, MD.)

agents such as cyclophosphamide, methotrexate, and azathioprine are reserved for patients with chronic nonsteroid-responsive disease, although there is little literature to fully support their use.[32]

## PULMONARY ALVEOLAR PROTEINOSIS

PAP is a rare disease first described by Rosen and colleagues in 1958.[35] The hallmark of this disorder is the thick, proteinaceous material that fills the alveolar spaces and impairs gas exchange. The disease is now recognized to exist in three forms: acquired, congenital, and secondary.[36] The acquired form represents over 90 percent of all reported cases[36] and is the type mainly discussed here.

Acquired PAP typically affects men in the fifth decade of life.[35,36] Symptoms tend to be gradual in onset, with a median of 7 months before diagnosis.[36] Common complaints include progressive dyspnea, cough, and fatigue.[37] Low-grade fevers have been reported, but higher temperatures suggest a superimposed infection.[37] Physical examination findings are nonspecific and frequently normal despite significant hypoxemia.[36] The radiographic appearance is nonspecific, with typically a bilateral alveolar filling process, but interstitial patterns can coexist or predominate.[36] HRCT scans show ground-glass opacification in a geographic pattern.[36] CT may also show interlobular thickening of the septa, producing a "crazy paving" pattern[36] (Fig. 5-10).

Historically, open lung biopsy was required for diagnosis.[36] However, more recent experience has shown that bronchoscopic techniques can reliably diagnose the majority of patients.[36,37] BAL produces a characteristic "milky" return, which represents the proteinaceous material that accumulates in the alveolar spaces.[36,37] Transbronchial biopsies have a high diagnostic yield as well.[37]

Treatment of PAP has been with whole-lung lavage under general anesthesia with a double-lumen endotracheal tube.[36,37] This procedure produces significant and durable improvements in clinical, physiologic, and radiographic parameters. However, the majority of patients will need repeated lavages over time.

Recent studies have found a link between granulocyte-macrophage colony-stimulating factor (GM-CSF) and PAP.[36] Initial studies found that GM-CSF "knockout" mice develop a lung disease similar to PAP. Further studies have found that most patients with acquired PAP have blocking antibodies to GM-CSF in lavage fluid and serum. These findings have led to the novel approach of using exogenous GM-CSF as treatment, with some success in small case series.

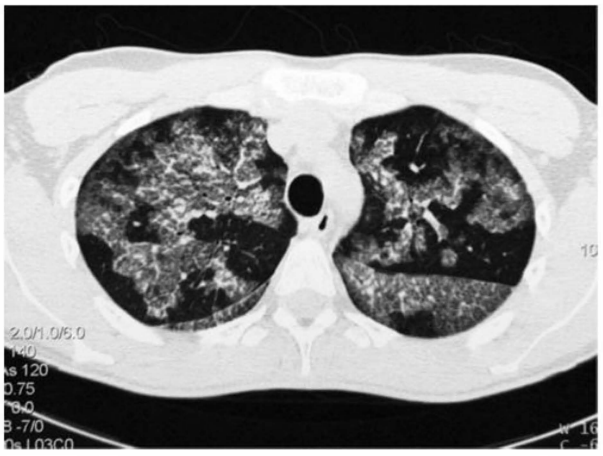


**FIGURE 5-10** Pulmonary alveolar proteinosis. Note bilateral infiltrates with a distinct appearance that has been described as "crazy paving."

## EOSINOPHILIC LUNG DISEASES

The eosinophilic lung diseases constitute a wide range of processes with a common finding of eosinophils in serum, lavage fluid, and/or on histology.[38] Early classifications included the syndrome of pulmonary infiltrates with eosinophilia (PIE); however, peripheral eosinophilia is variable in some processes and thus is not inclusive of the full range of diseases. The most current terminology is used here as a review of the important processes likely to be encountered. These include acute and chronic eosinophilic pneumonia (CEP), Churg–Strauss syndrome, and allergic bronchopulmonary aspergillosis (ABPA). A discussion of all the other diseases included in this category is beyond the scope of this chapter.

### Simple Eosinophilic Pneumonia (Löffler Syndrome)

Löffler syndrome was first described in 1932.[39] It consists of migratory pulmonary infiltrates and blood eosinophilia. Patients are typically asymptomatic or have only minimal symptoms.[39] Chest radiographs are usually described as a combination of interstitial and alveolar patterns that are migratory and peripherally located and often based in the pleura.[40] Infiltrates can be unilateral or bilateral.[40]

The underlying etiology, when found, has usually been linked to a parasitic infection.[38] *Ascaris* infection has classically been described. Drug reactions have also been found.

Patients typically have full resolution of radiographic and blood abnormalities within 1 month.[38] This resolution is usually spontaneous and rarely requires treatment with corticosteroids. Pathologic specimens are seldom required to confirm the diagnosis.

### Idiopathic Acute Eosinophilic Pneumonia

IAEP is a rare disease that has typically been reported in otherwise young, healthy individuals. Since the first reports in 1989, around 100 cases have been described.[41–43] This is a

diagnosis of exclusion with a characteristic presentation that includes an acute febrile illness (usually of less than 5 days' duration), bilateral infiltrates, hypoxemic respiratory failure, and significant BAL eosinophilia (>25 percent).[38,41–43] IAEP can easily mimic atypical pneumonia and acute respiratory distress syndrome (ARDS).

The typical presentation is that of a febrile illness with dyspnea, cough, myalgias, pleuritic chest pain, and respiratory distress.[38,41–43] Mechanical ventilation is frequently required. Chest x-rays invariably show bilateral infiltrates, which are usually diffuse and can be alveolar, interstitial, or a mixture of both. Only a minority of patients present with peripheral eosinophilia. However, the subsequent development of eosinophilia has been reported in as many as 68 percent of patients in one series.[43]

BAL is recommended in suspected cases to demonstrate the characteristic eosinophilia in the lavage fluid.[38,41–43] Eosinophil counts representing 40 to 50 percent of the differential is typical. When done, transbronchial biopsies and open lung biopsies have found varying stages of diffuse alveolar damage, including with marked interstitial and alveolar infiltration with eosinophils.[44] Because IAEP is a diagnosis of exclusion, the second role for lavage and/or biopsy is to rule out the presence of an underlying infectious etiology.

Treatment generally consists of corticosteroids with a relatively short duration. Patients will generally have a rapid response, with improvement within 1 to 2 days.[38] Relapse after discontinuation of steroids is not characteristic, and the absence of relapse has been suggested as a diagnostic criterion.[38] In one series, almost 25 percent of patients improved spontaneously without the use of corticosteroids.[43]

## Chronic Eosinophilic Pneumonia

Although this process was originally described by Christoforidis and Molnar in 1960,[45] most authors give the credit to Carrington and coworkers, who published the first large series in 1969.[46] As compared with acute eosinophilic pneumonia, CEP has a more subacute presentation and causes milder symptoms.

In one series of 107 patients, the average duration of symptoms before diagnosis was 7.7 months.[47] Patients tend to be in their fourth or fifth decade at presentation. A 2:1 female-to-male ratio has been noted.[47,48] A history of atopy occurs in one-half of patients, with asthma being the most common form.[47,48] Presenting complaints have included cough, fever, dyspnea, and weight loss.[47] Other notable symptoms seen in approximately one-third of patients include sputum production, wheezing, and night sweats.[47]

Diagnostic tests can be very helpful in the diagnosis of CEP. Peripheral eosinophilia is very common, occurring in 88 to 95 percent of patients, with a mean value of 26 to 32 percent.[47,48] Other laboratory values are also elevated, including erythrocyte sedimentation rates and serum IgE levels.[47,48] BAL contains very high levels of eosinophils, representing 25 percent to over 40 percent of the total cells.[38,48]

Chest radiography has classically been reported as showing the "photographic negative of pulmonary edema"[46] (Fig. 5-11A). However, a more recent series of patients have shown that only 25 percent have this finding.[47] The most common findings are peripheral bilateral infiltrates that were described as consolidated, ground-glass, or a mixture of both.[38,47,48] Upper lobe predominance is more common than lower lobe.[48] Migratory opacities, pleural effusions, and cavitation are uncommon.[38,47,48] CT sometimes helps to show the peripheral nature of the infiltrates.[38] Mediastinal adenopathy has been shown in 3 of 6 patients in one series[49] and 7 of 40 patients in another.[48]

Biopsy typically reveals intra-alveolar exudates rich with eosinophils and histiocytes.[38,46–48] The surrounding interstitium is frequently also infiltrated with eosinophils and histiocytes (Fig. 5-11B).[38,46–48] Approximately 50 percent of patients may also have interstitial fibrosis.[38,46–48] At times, mild vasculitis is seen.[38,46–48] Coexisting BOOP is also a frequent finding.[46–48]

Some authors suggest that patients with a typical clinical presentation and typical radiographic findings can be treated empirically.[47] Others would favor the addition of bronchoscopy with lavage to confirm the presence of increased eosinophils.[38] However, most favor empiric trials of corticosteroids. Patients typically show rapid improvement in symptoms, usually within 24 to 48 h, followed in time by radiographic resolution.[46–48] This rapid response is felt to be characteristic and confirms the diagnosis. The lack of a prompt response should suggest an alternative diagnosis and consideration of a biopsy.

Unlike acute eosinophilic pneumonia, CEP is characterized by a high rate of relapse when patients are weaned off of steroids.[46–48] Most authors have recommended prolonged courses of steroids, on the order of 6 months to 1 year. Although relapses are common, they respond well to increased doses of steroids.

## Pulmonary Langerhans Cell Histiocytosis (Eosinophilic *Granuloma*)

PLCH, also known as eosinophilic *granuloma* (EG), is a rare form of diffuse lung disease. Although most commonly found affecting the lungs solely, Langerhans cell histiocytosis can involve multiple organs including the bone, skin, pituitary gland, and other organs.[50] Langerhans cells are normally found in small numbers in the lung, where they function as antigen-presenting cells. In PLCH, the population of Langerhans cells is expanded, with destructive consequences for the parenchyma. The etiology for the expansion of this cell population is unknown.

Affected individuals tend to be in their third or fourth decade at the time of diagnosis.[51,52] The vast majority of patients diagnosed with PLCH are current smokers.[50–52]

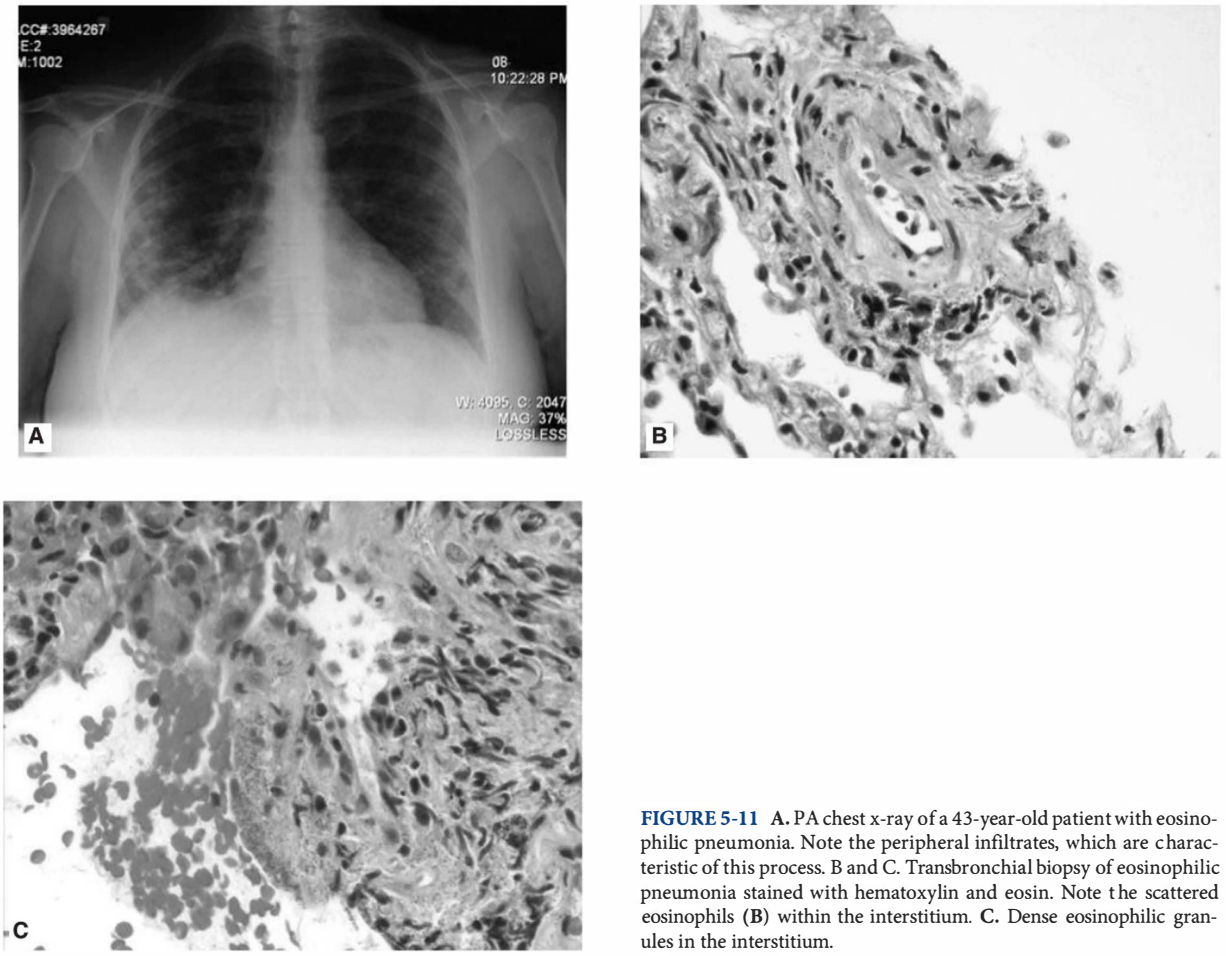



**FIGURE 5-11** **A.** PA chest x-ray of a 43-year-old patient with eosinophilic pneumonia. Note the peripheral infiltrates, which are characteristic of this process. B and C. Transbronchial biopsy of eosinophilic pneumonia stained with hematoxylin and eosin. Note the scattered eosinophils **(B)** within the interstitium. **C.** Dense eosinophilic granules in the interstitium.

At presentation, approximately one-fourth of patients will be asymptomatic.[50,51] Common symptoms include nonproductive cough, dyspnea with exertion, and pleuritic chest pain.[51] In one series, 11 percent of patients had experienced spontaneous pneumothorax.[51] Chest radiography typically reveals bilateral reticulonodular and interstitial infiltration with upper- and middle-lobe predominance.[50] Cystic changes are common and may be the predominant lesion in later stages of the disease.[50] Similar findings on CT, in the proper clinical context, are felt to be diagnostic, thus obviating the need for open lung biopsy.[50,53]

The course of the illness is highly variable. Most patients will have resolution of symptoms and radiographic abnormalities with smoking cessation, but a small percentage will go on to end-stage lung disease.[50,51] Corticosteroids have been variably used, but there is no consensus as to their utility. Lung transplantation has been advocated for patients with end-stage disease; however, there are reports of recurrence in the transplanted lung.[54]

## ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

ABPA occurs in up to 28 percent of patients with steroid dependent asthma and 15 percent of patients with cystic fibrosis.[55–57] The disease occurs when patients have a complex immune response to antigens expressed by *Aspergillus* that is colonizing the bronchial mucosa. Although most commonly associated with the fungus *Aspergillus fumigatus*, this allergic process has been described with other fungi including *Candida, Penicillium*, and other species of *Aspergillus*, including *A. flavus*.[55] The diagnosis of ABPA is based on a variety of clinical, radiographic, and laboratory findings. Suggested criteria include a history of asthma or cystic fibrosis, immediate cutaneous reactivity to *Aspergillus* species, an elevated total IgE (>1000 ng/mL), elevated serum IgE antibodies to *A. fumigatus*, precipitating antibodies to *A. fumigatus*, central bronchiectasis, and chest x-ray infiltrates. Striking peripheral blood eosinophilia is common as well as sputum cultures that grow *Aspergillus* species.

Symptoms commonly include wheeze, cough, fever, and anorexia.[55,57] Sputum production is also common with "dirty green" plugs. During an exacerbation chest radiography may reveal fleeting pulmonary infiltrates as well as dense infiltrates in central bronchioles giving rise to a "gloved finger" appearance.

Corticosteroids are the cornerstone of therapy to treat and reduce the frequency of exacerbations.[55–57] Most authorities recommend initial treatment for several months followed by a slow taper. Some patients will go into clinical remission but the majority will require continued long-term therapy for intermittent exacerbations. Recently several studies have suggested a role for the oral antifungal itraconazole as a steroid sparing agent.[58,59]

## HYPERSENSITIVITY PNEUMONITIS

HP is a clinically diverse disease process that results from the inhalation of a variety of antigens.[60–62] Farmer's lung is the classic example but numerous other examples of HP, also known as extrinsic allergic alveolitis, have been described.[60–62] The hallmark of this disease is an individual's immunologic response to an inhaled antigen. In order for HP to develop, first, the patient must be exposed to a potential antigen; second, the antigen must be of sufficiently small size (usually <3 μm) to travel through the respiratory tract and be deposited in an alveolus and distal bronchial tree; and third, there must be an immune response resulting in an inflammatory reaction.[60–62]

A multitude of exposures to a variety of antigens have been documented and described. Most forms of HP have been associated with antigens from fungi and bacteria such as *Mucor stolonifer,* which causes paprika slicer's lung in people who work with moldy paprika pods, and *Thermoactinomyces vulgaris,* which causes bagassosis in people who work with moldy sugarcane.[60] Pigeon breeder's lung is caused by exposure to animal proteins found in bird droppings, feathers, and serum.[60] A variety of chemicals have been implicated in HP, including hydrophthalic anhydride, which causes epoxy resin lung in people who work with heated epoxy resin.[60]

Although many people may be exposed to an antigen through occupation or hobbies, only a small percentage will go on to develop HP.[60–62] For example, in one study, only 8 percent of pigeon breeders in the Canary Islands were found to meet the criteria for pigeon breeders' lung.[63] In most studies, only 5 to 15 percent of exposed people go on to develop features of HP.[61] The host factors that determine whether an individual will develop an inflammatory reaction have yet to be determined.

HP has classically been subdivided into three forms: acute, subacute, and chronic.

### Acute Hypersensitivity Pneumonitis

The acute form of HP is thought to occur after a large inhalational exposure to an antigen. Characteristic symptoms include fever, chills, dyspnea, chest tightness, cough, and malaise.[60–62] Symptoms usually begin within 4 to 8 h of exposure and resolve 24 to 48 h later.[60–62] Patients typically describe similar symptoms after repeated exposures. Chest radiography can show diffuse ground-glass opacification or reticulonodular infiltrates[62] (Fig. 5-12). A lower-lobe predominance is common.[62] Lung function tests can reveal a restrictive defect as well as impaired diffusion.[61]

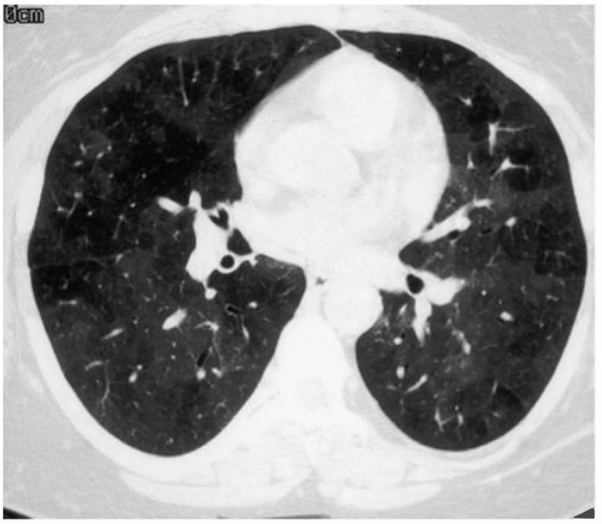


**FIGURE 5-12** Chest CT of a 45-year-old woman with acute hypersensitivity pneumonitis from exposure to a pet bird. Note bilateral "ground-glass" opacifications.

### Subacute and Chronic Hypersensitivity Pneumonitis

Unlike acute HP, subacute and chronic forms have an insidious onset of cough and dyspnea.[60–62] Other common symptoms include fatigue, malaise, and weight loss. Few authors make a distinction between subacute and chronic forms other than to suggest that patients with subacute HP can experience episodes of symptoms similar to acute HP.[61] A major difference between acute HP is the tendency to develop parenchymal fibrosis in some cases leading to end-stage lung disease. These patients can also develop right heart failure and digital clubbing.[60] Chest x-rays and CT in chronic forms have marked fibrosis and ground-glass attenuation[60–62] (Fig. 5-13). Centrilobular poorly defined micronodules are very suggestive of HP in both the acute and chronic forms.[60] Pulmonary function testing usually reveals restriction and decreased diffusion but a small percentage of patients have also been shown to develop an obstructive defect regardless of a smoking history.[60–62,64]

As there are no definitive tests, the diagnosis of HP is largely based on clinical presentation and history.[60–62,65] Suggested diagnostic criteria typically include (1) a history

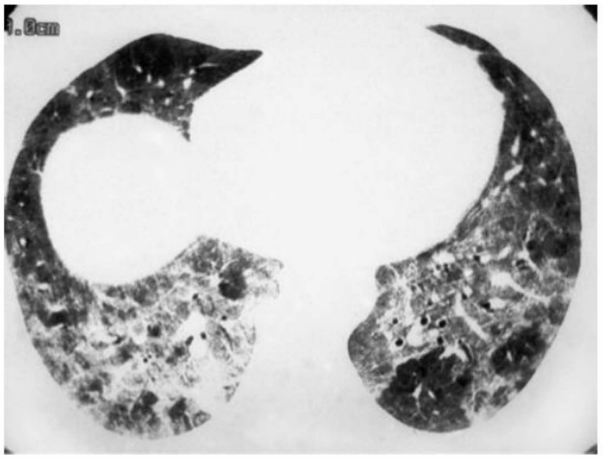


**FIGURE 5-13** Chest CT scan showing bilateral diffuse interstitial fibrosis with interspersed ground-glass opacifications from a patient with chronic hypersensitivity pneumonitis.

of exposure to a known antigen, (2) serum precipitating antibodies to the suspected antigen, (3) a history of common symptoms temporally related to antigen exposure, (4) an appropriate response to an inhalation challenge, (5) compatible results from radiographic and pulmonary function tests, and (6) granulomatous interstitial pneumonitis.[60–62,65] With this framework, several key points need further discussion.

A thorough history of possible exposures, occupational and domestic, is important to discern possible antigens. However, in regard to subacute and chronic forms, the insidious nature of the disease may prevent the identification of likely antigen.

Although supportive, the finding of precipitating antibodies is not diagnostic as a high number of exposed people will develop antibody responses but will not have detectable disease.[60–62] Alternatively, the absence of antibodies does not rule out HP owing to the lack of standardized antigen testing in laboratories.

Inhalational challenges, exposing the patient to the suspected antigen in either the natural environment or in a hospital setting and monitoring for a clinical response, have been used mainly in the research setting.[60]

Invasive diagnostic testing, including BAL and lung biopsy, is typically used in cases where the diagnosis is less apparent. BAL usually reveals a marked lymphocytosis with an inversion of the CD4 to CD8 ratio; however, this is variable and may depend on the type of HP and host factors.[60,62] The histology of HP can also be variable. Findings of cellular bronchiolitis, lymphoplasmacytic interstitial infiltrates, and poorly formed granulomas are considered typical.[62] However, multiple other patterns including UIP and NSIP have also been described.[60,62]

Most experts agree that the first goal of treatment is eliminating exposure to the inciting antigen.[60–62] However, repeated exposure to inhaled antigens does not necessarily lead to a chronic form with fibrosis but currently there is no way to predict that patients will have a progressive form of the disease.[60–62] There is no consensus for the use of corticosteroids.[60–62] A randomized controlled trial using corticosteroids in farmer's lung showed that corticosteroids lead to a more rapid improvement in pulmonary function, but there was no difference in outcomes at 5 years.[66] Interestingly, patients who were treated with corticosteroids tended to have more frequent episodes.[66]

## DRUG-INDUCED LUNG DISEASE

The true incidence of drug-induced lung injury is unknown, owing to the absence of definitive diagnostic studies and the high rate of underlying pulmonary diseases among patients, making it difficult to establish definitive causal relationships. Histologically, the majority of the injury patterns resemble those of disorders already discussed.[67–69] These include nonspecific interstitial pneumonia, organizing pneumonia, eosinophilic pneumonia, and HP. Other patterns of injury include diffuse alveolar damage, pulmonary hemorrhage, and edema. Two of the more common clinically encountered drug toxicities are discussed below.

### Methotrexate-Induced Lung Injury

The spectrum of methotrexate pulmonary toxicity is wide, including interstitial disease, pleural effusions, fibrosis, and noncardiogenic pulmonary edema.[67,70] The most commonly reported toxicity is an interstitial pneumonitis, which has been variably termed methotrexate pneumonitis, acute interstitial pneumonitis, and HP. The true frequency is unknown, with reports ranging from 2 to 10 percent of patients. It usually presents with subacute symptoms of cough, dyspnea, and low-grade fevers. Peripheral eosinophilia has been reported in up to 40 percent of patients. Pulmonary function tests typically reveal a restrictive pattern with a reduced diffusion capacity. Chest radiographs have usually shown a bilateral, predominantly basilar interstitial pattern. Alveolar and nodular patterns as well as pleural effusions and adenopathy have also been reported (Fig. 5-14). Lung biopsy reveals lymphocytic infiltration of the interstitium; granulomas and eosinophilia are seen in some cases (Fig. 5-15).

Methotrexate pneumonitis can occur at any time during therapy, and dose and route of therapy do not appear to predict its occurrence.[67,70] Most people will recover completely after cessation of the methotrexate. Corticosteroids are generally recommended for patients with significant impairment.

### Amiodarone Pulmonary Toxicity

Four clinical presentations of amiodarone pulmonary toxicity have been described: interstitial pneumonitis, ARDS, BOOP, and pulmonary nodules.[68,71] The most common is




**FIGURE 5-14** Methotrexate-induced lung injury showing bilateral pulmonary infiltrates with areas of consolidation on a background of increased interstitial markings.

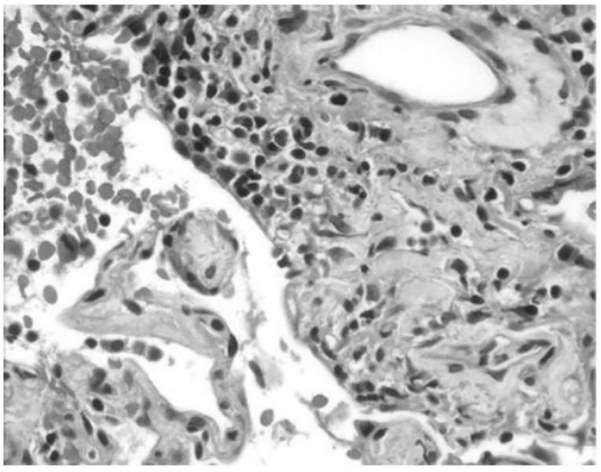


**FIGURE 5-15** Biopsy specimen of methotrexate-induced lung injury showing lymphocytic interstitial infiltrates with occasional eosinophils.

interstitial pneumonitis. The presentation is typically subacute, and it tends to occur after several months of therapy. Although it can occur at any dose, it does so usually in the context of a higher daily dosage (>400 mg/day). Patients' complaints frequently include cough, dyspnea, fever, and pleuritic chest pain.

There are no diagnostic studies for amiodarone pulmonary toxicity.[68,71] Laboratory studies are nonspecific but can show leukocytosis and elevated erythrocyte sedimentation rates. Pulmonary function studies reveal decreased diffusion capacity. Chest radiographs reveal patchy bilateral interstitial infiltrates. Lung biopsy is of limited value, as the findings are nonspecific. Alveolar accumulation of foamy macrophages occurs in people taking amiodarone with or without clinical disease. Other findings include type II pneumocyte hyperplasia and alveolar septal thickening.

Treatment consists of discontinuing amiodarone.[68,71] The majority of cases slowly resolve due in part to the prolonged half-life of the agent. Corticosteroids have had anecdotal success in some cases. For some patients in whom the use of alternative antiarrhythmic agents was not possible, a strategy of low-dose corticosteroids while continuing amiodarone has had some success.

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## BENIGN DIFFUSE PULMONARY DISORDERS BOARD REVIEW QUESTIONS (CHAPTER 5)

1. Which of the following is correct regarding idiopathic pulmonary fibrosis?
   A. There is a predominance of fibrosis in the subpleural and upper lung zones.
   B. It typically presents in the fifth decade of life with shortness of breath and a productive cough.
   C. Classic CT findings include traction bronchiectasis and honeycombing.
   D. Pulmonary function studies show an obstructive pattern with low DLCO.
   E. Transbronchial biopsies are usually adequate to establish the diagnosis.

2. Which is true regarding cryptogenic organizing pneumonia?
   A. The least common presentation is a nonresolving pneumonia.
   B. Significant leukocytosis is common.
   C. Frank hypoxemia is almost universal.
   D. Transbronchial biopsy is often insufficient to make the diagnosis.
   E. Treatment consists of steroid therapy over 2 to 3 months.

3. Which is correct regarding sarcoidosis?
   A. About 50 percent of cases will have pulmonary manifestations.
   B. The least common presentation is asymptomatic hilar adenopathy.
   C. Löfgren syndrome is an acute presentation characterized by erythema nodosum, polyarthralgias, and hilar adenopathy.
   D. The disease classically affects the lower and midlung zones.
   E. The histologic lesion is the caseating granuloma.

4. Which of the following is true regarding allergic bronchopulmonary aspergillosis?
   A. It occurs in nearly 30 percent of steroid-dependent asthmatics.
   B. The diagnosis is based on chest x-ray findings.
   C. IgA levels are elevated above 1000 ng/mL.
   D. Elevated peripheral blood eosinophilia is rare.
   E. Antifungals are the cornerstone of therapy.

5. Which is the most common presentation of amiodarone pulmonary toxicitiy?
   A. Pulmonary nodules
   B. BOOP
   C. ARDS
   D. Interstitial pneumonitis
   E. Pleural effusion

## ANSWERS

1. **Answer: C.** Classic CT findings of IPF include traction bronchiectasis and honeycombing. There is a predominance of fibrosis in the subpleural and lower lung fields. It typically presents in the seventh decade of life with shortness of breath and a dry, nonproductive cough. PFTs show a restrictive pattern with low DLCO. Transbronchial biopsies are usually inadequate because a larger tissue sample is necessary.
2. **Answer: D.** As a large tissue sample is necessary to make the diagnosis of COP/BOOP, transbronchial biopsy is often insufficiency. A nonresolving pneumonia is the most common presentation with only mild leukocytosis. Frank hypoxemia is rare. An extended period of steroid therapy over 6 to 12 months is the standard treatment.
3. **Answer: C.** Löfgren syndrome is an acute presentation of sarcoidosis characterized by erythema nodosum, polyarthralgias, and hilar adenopathy. Almost all cases will have pulmonary manifestations during some point of the disease process. The most common presentation is asymptomatic hilar adenopathy. Sarcoidosis classically affects the upper and midlung zones. The histologic lesion is the noncaseating granuloma.
4. **Answer: A.** Nearly 30 percent of steroid-dependent asthmatics will develop ABPA. The diagnosis is based on a combination of radiographs, clinical findings, and laboratory tests, including elevation of IgE levels above 1000 ng/mL. Striking peripheral blood eosinophilia is common. Corticosteroids are the cornerstone of therapy to treat and reduce the frequency of exacerbations.
5. **Answer: D.** Interstitial pneumonitis is the most common presentation of amiodarone pulmonary toxicity and tends to occur after several month of therapy in a subacute fashion.

# Thoracic Infections

*Kaushik Mandal*

6

**KEY CONCEPTS**

- The etiology and clinical manifestations of pneumonia depend on the environment where the disease is acquired and the host characteristics.
- Treatment of pneumonia is based on an assessment of place of therapy (outpatient, hospital ward, or ICU), the presence of coexisting cardiopulmonary diseases, and the presence of modifying factors.
- Although prompt initiation of antibiotics is critical in patients with nosocomial pneumonia, all patients with suspected pneumonia should have a sampling done of lower respiratory tract secretions to better guide the therapy.
- Lung abscess should be managed initially with appropriate medical therapy and/or percutaneous drainage.
- Owing to the presence of branching hyphae, infections due to actinomycosis and nocardiosis may be mistaken for fungal infections. It is important to make the distinction because actinomycotic infections do not respond to antifungal therapy but rather to antibiotics.
- Surgical consultation is regularly requested for the diagnosis and treatment of pulmonary complications of the endemic mycoses: *Histoplasma capsulatum, Blastomyces dermatitidis* and *Coccidioidomycosis immitis,* and the yeast *Cryptococcus neoformans*. All resemble pulmonary malignancies.
- Histoplasmosis causes pericarditis, mediastinal fibrosis, and mediastinal granuloma, which can cause entrapment of vascular structures, the esophagus, and the trachea.
- Coccidioidomycosis can cause both spontaneous pneumothorax associated with effusion and thin-walled cavities that can become superinfected with tuberculosis and aspergillosis.
- Cryptococcosis can result in organ damage from tissue distortion secondary to an expanding fungal burden.
- Most patients with pulmonary aspergillosis have either impaired immunity or underlying preexisting chronic lung disease. Aspergillomas may develop in preexisting cavities. Surgery is indicated for complications of the disease, such as massive hemoptysis.
- Surgery has largely been supplanted by multiple-regimen medical therapy for tuberculous and nontuberculous mycobacterial infections. There is still a role for pulmonary resection in multidrug-resistant infection, cavitary lesions, and lung destruction.

## PNEUMONIA AND LUNG ABSCESS

Lower respiratory tract infections are important in the practice of the thoracic surgeon because their complications may require surgical intervention and they may complicate thoracic surgical procedures.

### Pneumonia

Pneumonia is an infection of the lower respiratory tract that involves the terminal airways: respiratory bronchioles, alveolar ducts, and alveoli. The infection develops when the sterility of the tracheobronchial tree is breached by the introduction of a virulent pathogen or a defect in the host immunologic defense. Symptoms of acute lower respiratory infection may include fever or hypothermia, rigors, sweats, new cough with or without sputum production or change in color of respiratory secretions in a patient with chronic cough, chest discomfort, or shortness of breath. Most patients also have nonspecific symptoms, such as fatigue, myalgias, abdominal pain, anorexia, and headache.

Despite advancements in the diagnosis and treatment of pneumonia in the past century, it is listed by the Centers for Disease Control and Prevention as the sixth leading cause of death in the United States and the leading cause of death from infectious diseases.[1] Contemporary management of pneumonia is based on whether the infection was acquired in the community versus in the hospital, including any care

facility, the severity of illness, and the patient's comorbid conditions, including immune status.

## COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia (CAP) is commonly defined as an acute infection of the pulmonary parenchyma in a patient not hospitalized or residing in a long-term-care facility for ≥14 days before the onset of symptoms. CAP is among the leading causes of death in the United States, accounting for some 65,000 deaths in 2002[2]; it is responsible for more than 10 million physician visits a year and some 1.4 million hospital discharges. The most common etiologic agent of CAP is *Streptococcus pneumoniae,* which accounts for about two-thirds of all cases of bacteremic pneumonia.[2] Other pathogens include *Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Staphylococcus aureus, Streptococcus pyogenes, Neisseria meningitidis, Moraxella catarrhalis, Klebsiella pneumoniae* and other gram-negative rods, *Legionella* species, influenza virus (depending on the season), respiratory syncytial virus, adenovirus, and parainfluenza virus. Gram-negative bacilli (Enterobacteriaceae and *Pseudomonas*) are the cause of CAP in some patients (those who have had previous antimicrobial treatment or who have pulmonary comorbidities). The frequency of other causes, such as *Mycobacterium tuberculosis, Chlamydophila psittaci* (psittacosis), *Coxiella burnetii* (Q fever), *Francisella tularensis* (tularemia), and endemic fungi (*Histoplasma, Coccidioides, Blastomyces*) vary between epidemiologic settings.[3] Certain pathogens cause pneumonia more commonly among persons with specific risk factors. For instance, pneumococcal pneumonia is especially likely to occur in the elderly and in patients with a variety of medical conditions, including alcoholism, chronic obstructive airway disease, immune-deficiency, etc. *Legionella* is an opportunistic pathogen that is rarely recognized in healthy young children and young adults. *It is an important cause of pneumonia in organ transplant recipients* and in patients with renal failure.

All patients suspected to have pneumonia should undergo chest radiography for the following reasons: to confirm the diagnosis, to provide information on the location and extent of the disease, to explore the possibility of complications such as pleural effusion, multilobar disease, and cavitation; to detect underlying pulmonary disease or alternative diagnoses; and to monitor the progression or resolution of the disease.[4] Other appropriate tests for hospitalized patients with CAP include a complete blood cell count and differential, serum creatinine, blood urea nitrogen, glucose, electrolytes, and liver function tests. Oxygen saturation should be assessed by pulse oximetry in all admitted patients and arterial blood gas in sicker patients. There should be two pretreatment blood cultures as well as Gram's staining and culture of expectorated sputum.[4,5]

Other tests that should not be performed routinely but might be useful in some patients admitted to the hospital include the urinary antigen assays for *Legionella* species and *Strep. pneumoniae* and a direct stain (i.e., acid-fast) for the detection of mycobacterial infections in patients who are in high-risk categories for tuberculosis.[3,5] HIV serology with informed consent should also be considered, especially for persons aged 15 to 54 years.[3] Serologic testing may also include tests for viral agents, endemic fungi, and other unusual pathogens in appropriate clinical settings. Invasive diagnostic techniques (transtracheal aspiration, bronchoscopy with a protected brush catheter, bronchoalveolar lavage [BAL], and direct percutaneous fine-needle aspiration of the lung) are used to obtain lower airway specimens uncontaminated by oropharyngeal flora. These procedures may help to obtain early accurate diagnosis and are reserved for occasional patients who are severely ill.[1,5] Potentially infected body fluids from other anatomic sites—including pleural fluid, joint fluid, and cerebrospinal fluid (CSF)—should be obtained for chemistry, Gram's staining, and culture if warranted by the clinical presentation.

Pathogen-directed antimicrobial therapy is ideal, but this is usually not feasible because no etiology can be identified in more than 50 percent of cases. Empiric antibiotic regimens should include coverage of "atypical pathogens" and should be changed when results of culture and *in vitro* sensitivity tests become available.[3] All admitted patients should receive their first dose of antibiotic therapy within 8 h of arrival at the hospital. This has been shown to reduce mortality at 30 days.[6] The American Thoracic Society (ATS) currently makes recommendations based on an assessment of place of therapy (outpatient, hospital ward, or ICU), the presence of coexisting cardiopulmonary disease (chronic obstructive pulmonary disease [COPD], congestive heart failure), and the presence of modifying factors such as age, immune status, other comorbid factors, etc. Most patients can be treated using monotherapy with antipneumococcal fluoroquinolone except for ICU-admitted patients who should receive β-lactam plus either a macrolide or a quinolone. Appropriate at-risk patients should receive a regimen with two antipseudomonal agents.

## HOSPITAL-ACQUIRED (NOSOCOMIAL) PNEUMONIA

Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs 48 h or more after admission and that was not incubating at the time of admission. According to the report from the National Center for Infectious Diseases, nosocomial pneumonia is the most frequent hospital-acquired infection in the combined medical and surgical ICUs, which accounts for 31 percent of all infections in the ICU.[7] Risk factors for HAP include mechanical ventilation for >48 h, residence in an ICU, duration of ICU or hospital stay, severity of underlying illness, and presence of comorbidities. Generally, loss of mechanical host defense and suppression of normal flora probably explain a major component of the increased risk of pneumonia in hospitalized patients. The most obvious compromise of normal host immunity in hospitalized patients is alteration of the mechanical components of lung defenses.

Nearly half of the HAP cases are polymicrobial. Early-onset HAP (occurring in the first 4 days of hospitalization) is often caused by community-acquired pathogens such as *H. influenzae, Strep. pneumoniae*, or methicillin-susceptible *Staph. aureus* (MSSA). HAP developing ≥5 days after hospitalization ("late onset") is often caused by aerobic gram-negative bacilli (e.g., *Pseudomonas aeruginosa*, Enterobacteriaceae, or *Acinetobacter*) or methicillin-resistant *Staph. aureus* (MRSA).[8] In patients receiving mechanical ventilation, these antibiotic-resistant pathogens assume increasing importance. Other gram-negative rods, such as *Escherichia coli* and *Klebsiella* species, are also common pathogens. Nosocomial viral and fungal infections are uncommon causes of HAP in immunocompetent patients.

Ventilator-associated pneumonia (VAP) is a pneumonia that arises more than 48 to 72 h after endotracheal intubation. VAP accounts for as much as 83 percent of nosocomial pneumonia and carries a particularly poor prognosis, with a reported mortality rate of up to 50 percent. Aspiration of oropharyngeal or gastric contents contaminated with colonizing flora is important in the pathogenesis of VAP. Several factors that lead to impairments in level of consciousness and/or swallowing and cough reflexes (e.g., related to cerebrovascular disease) increase the risk for the development of aspiration pneumonia. The oropharynx appears to be the most important source of microorganisms. Continuous aspiration of subglottic secretions has been associated with significant reductions in the incidence of VAP in two randomized trials.[9] Supine patient positioning may also facilitate aspiration, which may be decreased by a semirecumbent positioning.[10] Enteral nutrition has been considered a risk factor for the development of pneumonia mainly because of an increased risk of aspiration of gastric contents. However, its alternative, parenteral nutrition, is associated with higher risks for infections associated with intravascular devices, complications of line insertions, higher costs, and loss of intestinal villous architecture, which may facilitate enteral microbial translocation. Nasogastric intubation and gastroparesis are other known risk factors for aspiration.

The diagnosis of HAP is suspected if the hospitalized patient has a radiographic infiltrate that is new or progressive along with clinical findings suggesting infection, which include the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation. Most studies of nonintubated patients have involved clinical diagnosis with sputum culture. A recent meta-analysis showed that the most acceptable standards for the diagnosis of VAP require quantitative cultures of BAL fluid or protected specimen brush samples. BAL is also recommended if the patient is already receiving antibiotics.

Initial inadequate antimicrobial therapy for HAP is an independent risk factor for increased mortality. Initial therapy (while awaiting results of cultures) must be empiric and cover a broad spectrum of possible pathogens. Demographics, host factors (e.g., severity and acuity of illness, comorbidities), duration of hospitalization, prior antibiotic use, and antimicrobial resistance patterns within the hospital or ICU must be taken into account in selecting antibiotics for empiric treatment. Rates of resistance are influenced by type and size of hospital, ICU or non-ICU setting, anatomic site of isolation, and patterns of prior antibiotic use within individual patients or institutions. Empiric treatment for pneumonia occurring within the first 4 days of hospitalization in patients without severe comorbidities or exposure to antibiotics need not encompass *P. aeruginosa* or potentially resistant pathogens. However, broader-spectrum coverage (to include these pathogens) is advised for critically ill ICU patients requiring prolonged mechanical ventilation or those who have received prior antibiotics. In this context, a combination of antipseudomonal β-lactam (e.g., cefotetan) plus an aminoglycoside (if no contraindications to aminoglycoside use exist) can be used. Alternatively, a fluoroquinolone can be substituted for the aminoglycoside. Linezolid is an alternative to vancomycin for the treatment of MRSA. The Study Group on Aspiration Pneumonia found that ampicillin plus the β-lactamase inhibitor sulbactam, when compared with clindamycin with the optional addition of a second- or third-generation cephalosporin, was equally effective in terms of clinical response.[10] Antibiotic therapy should be tailored appropriately when culture results become available.

## Lung Abscesses

### ETIOLOGY AND PATHOLOGY

Lung abscess is defined as necrosis of the pulmonary tissue caused by microbial infection and the formation of cavities containing necrotic debris or fluid. The process usually begins as a localized pneumonitis. Liquefaction necrosis of the lung tissue eventually communicates with the bronchial tree. This partial internal drainage results in the classic cavity with an air-fluid level. The formation of multiple small (<2 cm) abscesses is occasionally referred to as necrotizing pneumonia or lung gangrene. Both lung abscess and necrotizing pneumonia are manifestations of a similar pathologic process.

Aspiration of infectious material is the most frequent etiologic mechanism in the development of primary lung abscess. Poor oral hygiene, dental infections, and gingival disease are common in these patients. Some of the factors that predispose to aspiration include states of compromised consciousness (e.g., cerebrovascular accident, seizure, alcoholism, anesthesia, head trauma, and coma) and esophageal disease (e.g., achalasia, reflux disease, and various causes of esophageal obstruction). Immunocompromised hosts—including patients on various chemotherapies, malnourished patients, and those with multiple trauma—are also at risk. Secondary lung abscess can occur from a hematogenous source; bronchial obstruction by tumor, stricture, or foreign body; or extension from an extrapulmonary site, such as mediastinal, subdiaphragmatic, or hepatic abscesses.[11]

The posterior segment of the right upper lobe and the superior segment of the right lower lobe are the most

common locations for lung abscess. This is due to gravitation of the infectious material from the oropharynx into these dependent areas of the lung. Lung abscesses have numerous infectious causes. The dominant pathogens are *Peptostreptococcus, Bacteroides, Prevotella,* and *Fusobacterium* species.[12] A primary lung abscess may be caused by *Strep. pneumoniae, Strep. viridans, K. pneumoniae,* and *H. influenzae.* Selected nonbacterial pathogens that can produce lung abscess include parasites (e.g., *Entamoeba histolytica*), many fungi (e.g., *Aspergillus* species, *Histoplasma capsulatum*), and mycobacteria. A number of opportunistic infections, such as nocardiosis and aspergillosis, can dominate in lung abscess in immunocompromised hosts.

One unique mechanism for the development of lung abscesses occurs in Lemierre syndrome, or jugular vein suppurative thrombophlebitis.[13] This infection begins in the pharynx (sometimes with an overt tonsillar or peritonsillar abscess) but spreads to involve spaces in the neck and the carotid sheath, which contains the internal jugular vein. Bacteremia, due to *Fusobacterium necrophorum*, and septic emboli to the lungs, which subsequently cavitate, are all characteristic complications of this process once the vessels are involved. Tricuspid valve endocarditis, usually due to *Staph. aureus*, also typically causes septic emboli that are widely distributed in both lungs. This is a common feature of endocarditis complicating injection drug use and an infrequent complication of septic venous thrombosis in other settings.

## CLINICAL PRESENTATION

Most of these patients present with a subacute onset of illness and do not seek medical attention for 2 weeks or more after the onset of illness. Early symptoms are often those of pneumonia—that is, malaise, anorexia, sputum-producing cough, sweats, and fever. Initially, foul sputum is not observed in the course of the infection; however, after cavitation occurs, putrid expectorations are quite prevalent. The odor of breath and sputum of a patient with an anaerobic lung abscess is often quite pronounced and noxious and may provide a clue to the diagnosis. Hemoptysis may occasionally follow the expectoration of the putrid sputum. The sputum may contain gangrenous lung tissue. Chest pain, if present, usually indicates pleural involvement.

On physical examination, a small area of dullness, indicating localized pneumonic consolidation, is found, and usually suppressed (rather than bronchial) breath sounds. Fine or medium moist crackles may be present. If the cavity is large, there may be tympany and amphoric breath sounds. Signs of pulmonary suppuration generally disappear with appropriate antibiotic therapy, but this disappearance does not necessarily denote cure. If the abscess becomes chronic, weight loss, anemia, and hypertrophic pulmonary osteoarthropathy may occur. Physical examination of the chest may be negative in the chronic phase, but rales and rhonchi are usually present.

## DIAGNOSIS

Chest x-rays early in the course may show a segmental or lobar consolidation, which sometimes becomes globular as pus distends it. The distinctive characteristic of lung abscess, the air-fluid level, can be observed only on a chest x-ray film taken with the patient upright or in the lateral decubitus position (Fig. 6-1). In the presence of associated pleural thickening, atelectasis, or pneumothorax, the air-fluid level may be obscured. A computed tomography (CT) scan of the chest is valuable for better anatomic interpretation. It can demonstrate cavitation within an area of consolidation, the thickness and regularity of the abscess wall, and the exact position of the abscess with regard to the chest wall and bronchus.

The indications and comparative benefits of invasive procedures such as transtracheal aspirates, transthoracic aspirates, and fiberoptic bronchoscopy are controversial and depend to a great extent on operator ability. The use of these methods to obtain appropriate culture specimens should be strongly considered in patients who do not respond to medical therapy within 2 weeks. However, dependable microbiologic data can be obtained only if these procedures are performed prior to the institution of antibiotic therapy. Most pulmonologists believe that these diagnostic procedures should not be performed routinely in all patients but should be reserved for patients with atypical presentations or unclear diagnoses. Bronchoscopy may also be used to exclude the presence of a foreign body or neoplasm and can provide drainage. These invasive procedures should be avoided in patients with coagulation disorders or bleeding tendencies and in those for whom it is difficult to provide adequate oxygenation.

Lesions that simulate bacterial lung abscess include cavitating bronchogenic carcinoma, bronchiectasis, empyema secondary to a bronchopleural fistula, tuberculosis, coccidioidomycosis and other mycotic lung infections, infected pulmonary bullae or air cysts, pulmonary sequestration, silicotic nodules with central necrosis, subphrenic or hepatic (amebic or hydatid) abscesses with perforation into a bronchus, and Wegener's granulomatosis. Detailed history, repeated clinical evaluation, and the procedures described above can usually differentiate these disorders from simple lung abscess.

## MEDICAL TREATMENT

Appropriate use of antibiotics determines morbidity and mortality in patients with lung abscess. Clindamycin is currently the first choice for the treatment of anaerobic infections; penicillin is a less-favored alternative. The Study Group on Aspiration Pneumonia[14] also included patients with primary abscesses and found that ampicillin plus the β-lactamase inhibitor sulbactam, as opposed to clindamycin, with the optional addition of a second- or third-generation cephalosporin, was equally effective in terms of clinical response. For gram-negative organisms as well as *Pseudomonas*, aminoglycosides and quinolones or cephalosporins can be used. Nafcillin or oxacillin or cephalexin

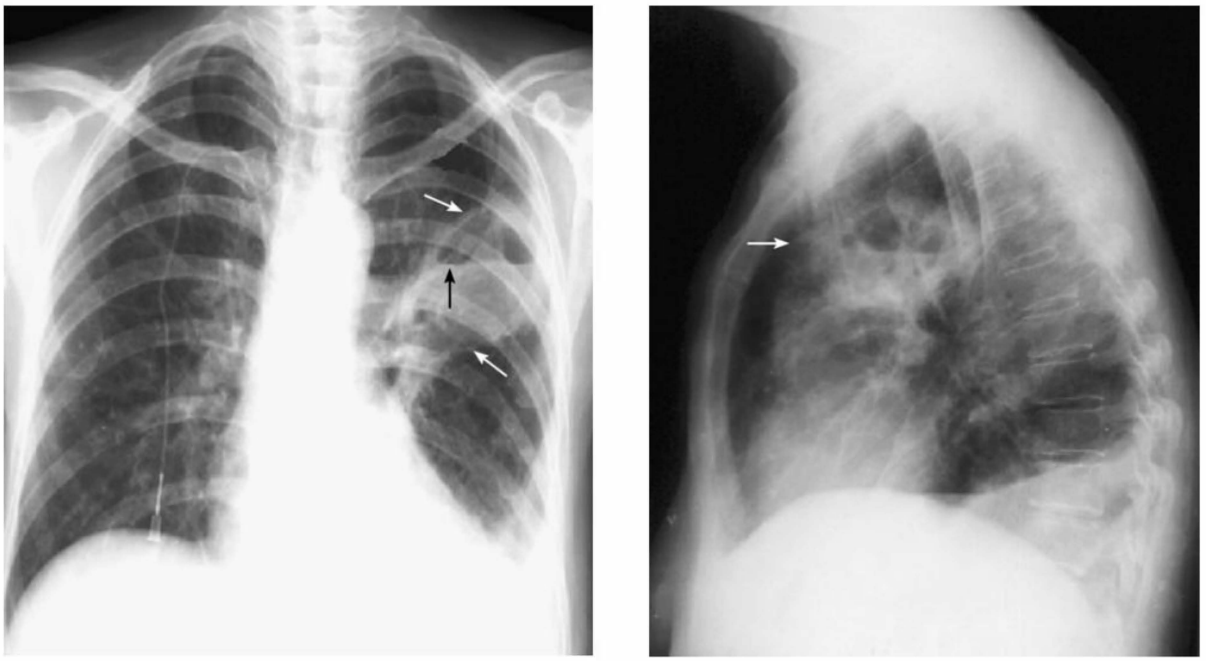


**FIGURE 6-1** Posteroanterior and lateral chest x-ray views of a patient with lung abscess. A well-defined area of increased transparency can be seen in the left upper lobe (white arrow). More than half of the cavity is filled with fluid and air (black arrow).

is recommended as a first-line agent for gram-positive organisms. The supportive treatment should include chest physiotherapy with postural drainage as well as nutritional support. Serial radiographs have limited use in the evaluation of response to therapy.

## SURGICAL TREATMENT

The availability of effective antibiotic therapy for primary lung abscess has drastically modified the natural history of the disease and diminished the role of surgery. Operative indications are less frequent in current practice, and these procedures are undertaken electively for chronic illnesses only after medical therapy has been unsuccessful. Prior to any surgical intervention, major considerations in patients with a delayed medical response include:

- An associated condition that precludes response, such as obstruction with a foreign body or neoplasm
- Erroneous microbial diagnosis with infection due to bacteria, mycobacteria, or fungi that have not been suspected and are not being treated
- Large cavity size (usually >6 cm in diameter) that may require prolonged therapy or empyema, which necessitates drainage
- An alternative, nonbacterial cause of cavitary lung disease, such as cavitating neoplasm, vasculitis, or pulmonary sequestration
- Other causes of persistent fever, such as drug fever or *Clostridium difficile*–associated colitis

***External Drainage.*** Indications for drainage include ongoing sepsis despite adequate antimicrobial therapy, progressively enlarging lung abscess in imminent danger of rupture, failure to wean from mechanical ventilation, and contamination of the opposite lung. In current practice, due to advances in interventional radiology, most of these lung abscesses are drained percutaneously under CT, ultrasound, or fluoroscopic guidance with acceptable success rates and morbidity.[15] This approach may be problematic in patients with coagulopathies if a significant amount of lung tissue must be traversed and other anatomic structures do not allow for unimpeded access to the cavity; another difficulty is posed by the presence of material within the abscess that cannot be effectively evacuated through a drainage tube. In addition, there is always a concern for soiling the pleural space with abscess contents. Direct tube drainage may be indicated in severely ill patients with large abscesses. Safe and effective pneumonostomy or cavernostomy with direct drainage (Monaldi procedure) depends on accurate topical localization of the abscess and a high degree of certainty that the underlying lung is firmly adherent to the overlying parietal pleura.

Endoscopic drainage of lung abscesses has also been reported with acceptable outcomes.[16] The procedure is performed by placing a pigtail catheter into the abscess cavity under bronchoscopic visualization and leaving the catheter in place until the cavity has drained. It can be considered in selected patients who have an airway connection to the abscess or in whom an endobronchial obstruction that prevents drainage is present.

***Surgical Resection.*** Surgical resection is now required in less than 10 percent of the cases of lung abscess. Indications for surgical intervention include unsuccessful medical management over a period of 8 weeks; complications such as bronchopleural fistula, empyema, massive or significant recurrent hemoptysis, and the persistence of a cavity larger than 6 cm after 8 weeks of treatment; necrotizing infection associated with multiple abscesses; and rupture into the pleural cavity with pyopneumothorax. Surgical intervention may also be indicated when there is a strong suspicion of carcinoma present. Intraoperatively, the patient will require double-lumen intubation or a bronchial blocker to help prevent spillage of pus into the contralateral lung, and rigid bronchoscopy may be indicated. Careful dissection and meticulous hemostasis are very important because of the adhesions and distorted anatomy caused by the abscess. Suction decompression of large cavities prior to dissection is usually helpful. Lobectomy is typically required, as segmentectomy may be inadequate and pneumonectomy is rarely necessary. Complete resection of involved areas as well as placement of two large-caliber tubes will help to speed recovery, prevent recurrence, and avoid the development of empyema.

## ACTINOMYCOTIC INFECTIONS

Owing to the presence of branching hyphae, infections due to actinomycosis and nocardiosis may be mistaken for fungal infections. It is important to make the distinction because actinomycotic infections do not respond to antifungal therapy but rather antibiotics.

### Actinomycosis

#### ETIOLOGY AND PATHOLOGY

Actinomycosis is a relatively uncommon subacute-to-chronic disease characterized by the production of suppurative abscesses or granulomas that eventually develop draining sinuses and dense scarring. These lesions discharge pus containing the organisms, which are filamentous, gram-positive, anaerobic-to-microaerophilic bacteria that are not acid fast. The branching form of the bacterium allows it to be recognized by the presence of "sulfur granules," or masses of hyphae, in the pus. In humans, actinomycosis is usually caused by *Actinomyces israelii,* which is a commensal in the normal human oropharyngeal flora. Areas of clinical manifestations of actinomycosis include cervicofacial, thoracic, and abdominal sites. Cervicofacial is the most common, comprising up to 50 percent of reported cases. Infections in the soft tissues of the mouth and throat can manifest themselves as submandibular masses with chronic draining sinuses. The infection can spread by direct extension from the neck across fascial planes into the mediastinum. Interestingly, there does not seem to be any greater incidence of the disease in patients who are immunocompromised, including those with HIV, patients who have undergone organ transplantation, or those on steroids.[17] Lung infection can result from dental surgery or aspiration and after trauma, including introduction of the organism from esophageal perforation. Hematogenous spread from distant lesions is also possible and can infect preexisting cavitary disease in the lung.

#### CLINICAL PRESENTATION

Thoracic actinomycosis commonly presents as a pulmonary infiltrate or mass that, if left untreated, can spread to involve the pleura, pericardium, and chest wall with rib osteomyelitis. The patient may have any combination of the nonspecific symptoms, such as fever, dry or productive cough, blood-streaked sputum, shortness of breath, chest pain, weight loss, fatigue, and anorexia. Physical examination may reveal abnormal breath sounds. The presence of sinus tracts with drainage from the chest wall (i.e., pleurocutaneous fistula) should raise very high clinical suspicion.

#### DIAGNOSIS

Definite diagnosis can be made by histopathologic examination and anaerobic culture of material from draining sinuses and abscesses. The "sulfur granules" are practically pathognomonic; they are approximately 1 mm in diameter and can be seen by the naked eye as yellowish particles. Microscopically, they are composed of branching filamentous rods that stain positive on Gram's stain (Fig. 6-2). On chest x-ray, the presence of a mass-like lesion that extends across fissures or pleura, invades into the adjacent chest wall or thoracic vertebrae, or causes local destruction of the ribs or sternum suggests thoracic actinomycosis. CT scans usually reveal an infiltrative mass with focal areas of decreased

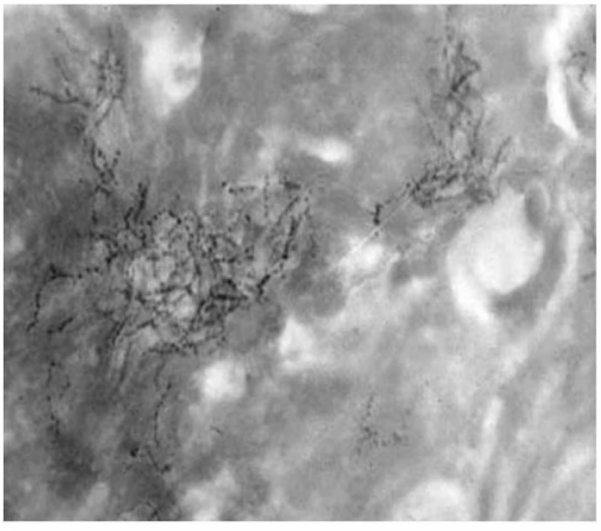


**FIGURE 6-2** Characteristic actinomycetic granules.

attenuation that enhance with contrast. This infiltrative mass has a tendency to invade surrounding tissues, and lymphadenopathy is uncommon.

### MEDICAL TREATMENT

High-dose penicillin, administered over a prolonged period, is the cornerstone of therapy for actinomycosis. Prolonged treatment is necessary owing to the presence of surrounding dense fibrous tissues. Lack of a clinical response from a patient receiving penicillin therapy may also indicate the presence of resistant companion bacteria, which may require modification of the antibiotic regimen.

### SURGICAL TREATMENT

Surgical intervention may be implemented for drainage of an abscess or empyema and for radical excision of sinus tracts when feasible. The most common indication for surgery is exploratory thoracotomy to rule out carcinoma.[18] Rarely, actinomycosis may be complicated by an unusual but significant hemoptysis—another indication for surgery—although selective bronchial artery embolization is a viable option in this setting. Even if histology suggests complete resection, it must still be followed by prolonged antibiotic therapy, as surgery alone is usually not curative. Inadequate antibiotic therapy postoperatively may result in complications such as bronchopleural fistulas and empyema.

## Nocardiosis

### ETIOLOGY AND PATHOLOGY

Nocardiosis is an acute, subacute, or chronic suppurative infection caused by weakly gram-positive, filamentous bacteria found worldwide in soils. *Nocardia asteroides* (80 percent) and *Nocardia brasiliensis* are the principal causes of human disease. *Nocardia farcinica* is being recognized with increasing frequency. The disease has a pronounced tendency toward remission and exacerbation, and infections are localized or disseminated. Localized infection usually manifests itself as primary cutaneous or, rarely, lymphocutaneous disease. Nocardiosis is an opportunistic infection, and disseminated or fulminant disease mainly occurs in immunocompromised hosts with underlying illnesses such as chronic granulomatous disease and HIV infection as well as patients on immunosuppressive therapy.[19] Lung transplant recipients have a particularly high incidence. Inhalation of the free-living organism is the likely route of infection. Introduction of *N. asteroides* via the respiratory tract results in pulmonary lesions, most often manifest as multiple abscesses. *Nocardia* abscesses are characteristically confluent, with little evidence of encapsulation, which probably accounts for the ready dissemination from the initial pulmonary focus. This organism also evades the host's bactericidal mechanisms. The primary disease, which occurs in the pulmonary system, may mimic tuberculous, staphylococcal, or mycotic infection. Hematogenous dissemination to the brain, kidneys, and liver are the most common metastatic sites.

### CLINICAL PRESENTATION

Symptoms in patients with nocardiosis are indistinguishable from those in patients with similar pulmonary infections of other microbial etiology. Cough with sputum production and fever are the dominant symptoms. Subcutaneous abscesses and draining sinuses near the chest wall that contain sulfur granules, similar to those observed in actinomycosis, are characteristic. Lung examination may reveal diffuse or localized abnormal breath sounds.

### DIAGNOSIS

The diagnosis of nocardiosis is established by aerobic culture of the causative organism from the site(s) of infection. Because *Nocardia* organisms grow more slowly than common bacteria, the microbiology laboratory should always be notified when nocardiosis is clinically suspected, especially if sputum is submitted. Bronchial brushings or percutaneous transthoracic needle aspiration biopsy of the lung may help to obtain appropriate samples and avoid the need for thoracotomy. *Nocardia* organisms are not demonstrated with routine hematoxylin and eosin (H&E) stain and may be seen only by a careful search of sections stained with Gram's, *Gomori methenamine silver* (GMS), or acid-fast bacillus stain.

Possible findings on chest x-ray and/or CT scan include irregular nodules (which may cavitate), reticulonodular or diffuse alveolar pulmonary infiltrates, lung abscess formation, and pleural effusion. All patients with pulmonary nocardiosis should have brain imaging by either CT scan or magnetic resonance imaging (MRI).[20]

### MEDICAL TREATMENT

Sulfonamides are first-line antimicrobial therapy and sulfadiazine is generally preferred because of its central nervous system (CNS) and CSF penetration. The combination of trimethoprim/sulfamethoxazole (TMP/SMX) or minocycline in high doses is an acceptable alternative. Treatment for a minimum of 2 to 3 months is recommended; treatment for as long as 12 months may be necessary, especially for systemic disease. Prophylactic TMP/SMX should be considered in transplant centers with excess rates of nocardial infection.[21]

### SURGICAL TREATMENT

Surgical intervention may be required for the drainage of lung abscess or empyema or when the diagnosis of a lung lesion is unclear. Pulmonary resection for previously diagnosed *Nocardia* infection is rarely indicated.

# MYCOTIC THORACIC INFECTIONS

## Histoplasmosis

### ETIOLOGY AND PATHOLOGY

Pulmonary manifestations are the hallmark of histoplasmosis, as this, also known as Darling disease, is probably the most common of all fungal infections of the lungs. Clinical syndromes range from asymptomatic infection to diffuse alveolar disease causing respiratory difficulty and occasionally death. *H. capsulatum* is a dimorphic fungus that remains in a mycelial form at ambient temperatures and grows as yeast at body temperature in mammals. Although the fungus can be found in temperate climates throughout the world, it is endemic to the Ohio, Missouri, and Mississippi River valleys in the United States. Farmers, construction workers, and people who enjoy outdoor activities are the most at risk. The disease results from aerosolization of conidial and mycelial fragments from contaminated soil due to the excreta of chickens, pigeons, and bats, which are then deposited in the alveoli. Conversion from the mycelial to the pathogenic yeast form occurs intracellularly. The host defense includes the fungistatic properties of neutrophils and macrophages. T-lymphocytes are crucial in limiting the extent of infection. Susceptibility to dissemination is increased markedly with impaired cellular host defenses.

### CLINICAL PRESENTATION

There is a wide spectrum of pulmonary histoplasmosis syndromes. The extent of disease and mode of presentation following initial exposure correlate with the size of the inoculum that was inhaled and the *Histoplasma*-specific immunity of the exposed subject. Pulmonary auscultation reveals nonspecific rales, wheezes, or findings consistent with the extent of underlying pneumonitis, consolidation, or cavitation.

***Asymptomatic Infection.*** Approximately 85 to 90 percent of infected immunocompetent individuals are asymptomatic. As the cell-mediated host immunity matures, delayed-type hypersensitivity to histoplasmal antigens occurs (3 to 6 weeks after exposure). The skin antigen test for *Histoplasma* species turns positive. Over weeks to months, the inflammatory response produces calcified fibrinous granulomas with areas of caseous necrosis. Most asymptomatic cases are now identified by the incidental finding of enlarged mediastinal or hilar lymph nodes or pulmonary nodules seen on radiographs or CT scans obtained for the evaluation of other conditions. Perhaps the main significance of such findings is the need to differentiate them from malignancy (Fig. 6-3).

***Acute and Subacute Pulmonary Histoplasmosis.*** Inhalation of a large amount of inoculums results in an inflammatory response in the lung and adjacent lymph nodes, similar to the Ghon complex of pulmonary tuberculosis.[22] This can be due to primary infection or reinfection. Nonimmune subjects usually present within 2 weeks with respiratory symptoms and diffuse pulmonary involvement radiographically. Fever, headache, malaise, myalgia, abdominal pain, and chills are common symptoms. Enlarged hilar and mediastinal lymph nodes (mediastinal lymphadenitis) are present in 5 to 10 percent of patients. Mediastinal histoplasmosis results in fibrosing mediastinitis, which can cause symptoms of compression and is the most frequent benign etiology of superior vena cava (SVC) obstruction. Cough, hemoptysis, dyspnea, and/or chest pain may be present; these are related to the degree of compression imposed on the pulmonary airway and circulation. Rarely, compression of the esophagus occurs, which causes dysphagia.

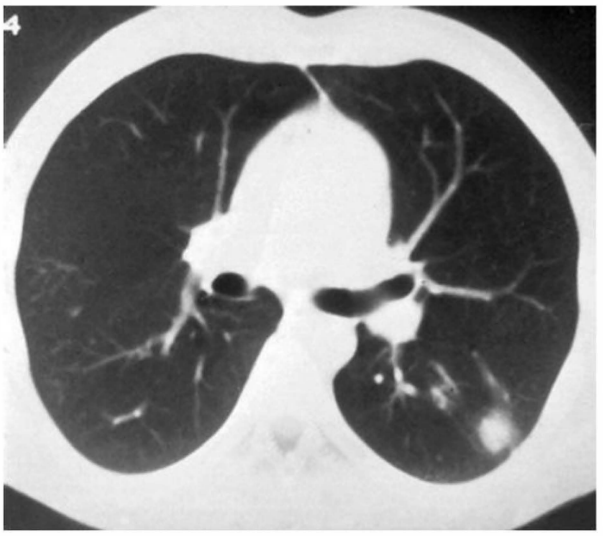


**FIGURE 6-3** Single pulmonary nodule in a patient with histoplasmosis.

***Chronic Pulmonary Histoplasmosis.*** This form occurs mostly in middle-aged men with underlying pulmonary disease (e.g., COPD); it is rare in children and represents 10 percent of symptomatic cases. Chronic pulmonary histoplasmosis (CPH) resembles reactivation tuberculosis, which is a common misdiagnosis. It is associated with cough, dyspnea, chest pain, weight loss, fevers, malaise, and night sweats. The clinical course of untreated CPH is progressive, with spread to contiguous lung. Complications, such as hemoptysis and bronchopleural fistulas, may ensue. Other infections can coexist, such as mycobacterial and other fungal infections (e.g., aspergillosis). Concurrent neoplasia is not uncommon.

Radiographs typically show changes of emphysema. Airspace opacities are present and may surround preexisting bullae, producing the appearance of cavitation with air-fluid levels. In severe cases the lung disease may progress and produce diffuse confluent airspace disease. As the patient recovers, the opacities on chest x-ray become more defined and nodular in appearance. The disease is almost always in the upper lobes and may be bilateral or unilateral in distribution. The inflammatory process progressively destroys lung tissue

and retracts the hilar structures upward as a consequence of the loss of lung volume. Pleural thickening adjacent to the lung disease is often present. Untreated cases may lead to progressive pulmonary fibrosis, which may result in respiratory and cardiac failure and recurrent infections.

***Progressive Disseminated Histoplasmosis.*** This form occurs mostly in hosts who are immunocompromised and probably results from a failure to develop protective cellular immunity following the acute infection. Symptoms vary depending on the duration of illness. Evidence for dissemination includes hepatosplenomegaly, extrapulmonary lymphadenopathy, mucosal or skin lesions, anemia, leukopenia, thrombocytopenia, or hepatic enzyme elevation. Furthermore, gastrointestinal involvement may produce diarrhea and abdominal pain. Cardiac involvement resulting in valvular disease, cardiac insufficiency, or vegetations may cause dyspnea, peripheral edema, angina, and fever. CNS involvement may produce headache, visual and gait disturbances, confusion, seizures, altered consciousness, and neck stiffness or pain. Note that subacute progressive disseminated histoplasmosis results in adrenal infection in 80 percent of patients. Radiographically, localized, cavitary, or miliary infiltrates as well as mediastinal lymphadenopathy may be present. The presence of calcified lymph nodes and lung granulomas suggests that disseminated disease has resulted from reinfection. Diffuse nodular opacities can be seen on CT scan (Fig. 6-4).

## DIAGNOSIS

Histoplasmin skin testing is not recommended for diagnostic purposes because of the high rate of positive reactions in endemic areas and the wide variability of response. *H. capsulatum* can be recovered from sputum, BAL fluid, lesions, blood, or bone marrow on routine fungal cultures; but the organism grows slowly and plates must be kept up to 12 weeks. The combination of blood and bone marrow cultures increases the likelihood of positive results. In chronic or severe acute pulmonary disease, organisms can be cultured from sputum or bronchial washings. Multiple specimens increase yield. Antibody testing can be performed using immunodiffusion, complement fixation, and radioimmunoassay in increasing order of sensitivity.

Antibody levels peak 6 weeks following exposure and decline over a 2- to 5-year period. Antigen detection in serum and urine is useful in immunocompromised individuals, whose ability to produce antibodies may be impaired. Cross-reactivity with antigens from *Blastomyces dermatitidis* and *Coccidioides immitis* may cause a false-positive test result. Urine specimens have higher sensitivity, up to 90 percent for disseminated disease. Paired urine and serum specimens have the highest yield. Note that some patients with acute histoplasmosis may have high serum levels of angiotensin-converting enzyme. This may cause a diagnostic confusion with sarcoidosis, especially if the patient also has hilar adenopathy.

Tissue may have to be obtained from pulmonary lesions and lymph nodes by bronchoscopy, percutaneous needle biopsies, or rarely, thoracoscopy in order to make the diagnosis. Histologic findings in pulmonary histoplasmosis demonstrate a predominantly mononuclear infiltrate. Multiple caseating granulomas are characteristic, with multinucleated giant cells and possible peripheral fibrosis and central calcification. On H&E staining, the yeast form of *H. capsulatum* has a false capsule. Special stains, such as GMS or periodic acid-Schiff (PAS), may reveal budding yeast, but the organisms can be mistaken for *Pneumocystis carinii* and other fungal organisms. In chronic pulmonary forms—in addition to underlying lung disease—vascular involvement, tissue necrosis, and scarring are present. Extensive fibrosis with collagen deposition is observed in fibrosing mediastinitis.

Echocardiography, CT scan of the abdomen, as well as CT scan and MRI of the brain should be performed when involvement of these areas is suspected. Lumbar puncture (LP) in CNS histoplasmosis demonstrates a lymphocytic pleocytosis, with elevated protein and normal or low glucose.



**FIGURE 6-4** Chest CT in progressive histoplasmosis, showing diffuse pulmonary nodules.

## MEDICAL TREATMENT

No treatment is needed for asymptomatic immunocompetent individuals without serious underlying disease. The antifungal therapy of choice is amphotericin B or its liposomal formulation for disseminated disease. The recommended duration of therapy is 12 weeks for acute and subacute histoplasmosis, 12 to 24 months for chronic disease, and 6 to 18 months for disseminated progressive disease. Patients with disseminated disease and HIV should be on treatment for life. Itraconazole can be used for those with moderate illness and for completion of therapy after response to amphotericin. In those who are hypoxic corticosteroids should be added. Mediastinal and hilar lymphadenopathies usually resolve. Granulomatous inflammation causes extensive enlargement with caseating necrosis, which may fibrose

with progressive healing. Occasionally, the lymph nodes may remain enlarged, compressing surrounding structures and distorting anatomic architecture.

### SURGICAL TREATMENT

Indications for surgery include:

- The presence of persistent or progressive cavitations with repeated relapses despite multiple courses of intensive medical treatment
- Medical therapy is insufficient to alleviate the compressive effects of progressive fibrosis, calcification, and scarring:
  - Life-threatening tracheobronchial and esophageal obstruction and bronchoesophageal fistula
  - SVC syndrome, pulmonary vascular obstruction, or middle-lobe syndrome associated with fibrosing mediastinitis
- Severe valvular insufficiency due to involvement in disseminated histoplasmosis
- Symptomatic broncholithiasis (which occurs when a calcified node erodes into a bronchus) if bronchoscopic extraction was unsuccessful

During surgery, care should be taken to avoid spilling necrotic material into the mediastinum and initiating a further fibrotic reaction.

## Aspergillosis

### ETIOLOGY AND PATHOLOGY

Pulmonary aspergillosis comprises a spectrum of mycotic diseases caused by *Aspergillus* species. Human illness is usually caused by *Aspergillus fumigatus* and Aspergillus niger and, less frequently, by Aspergillus flavus and Aspergillus clavatus. The transmission of fungal spores to the human host is via inhalation. *A. fumigatus* exists in two forms: (1) conidiophores, the reproductive forms that produce and release thousands of spores and (2) hyphae, which represent mature spores characterized by a 45-degree dichotomous branching pattern. The fungus grows widely in soil, water, and decaying vegetable or animal material. The spores are readily inhaled, and the fungus is commonly found in the sputum of healthy individuals.[23] Most patients with pulmonary aspergillosis have either impaired immunity or underlying preexisting chronic lung disease such as bronchiectasis, COPD, or tuberculosis. Impaired immunity may be secondary to alcoholism, advanced age, poorly controlled diabetes mellitus, underlying malignancy, cirrhosis, malnutrition, sepsis, AIDS, or organ transplantation.

### CLINICAL PRESENTATION

Pulmonary aspergillosis may present as any of three distinctive clinical syndromes: allergic bronchopulmonary aspergillosis, aspergilloma, and invasive aspergillosis.

***Allergic Bronchopulmonary Aspergillosis.*** Allergic bronchopulmonary aspergillosis (ABPA) represents a hypersensitivity reaction to *A. fumigatus* in patients with poorly controlled asthma or cystic fibrosis. It is associated with a type I, III, or IV allergic response to *Aspergillus* antigens. Excessive mucus production in association with impaired ciliary function leads to mucoid impaction of the airways. The plugs of inspissated mucus contain hyphal elements of *A. fumigatus* and eosinophils, but the organisms remain within the bronchial lumen; this feature differentiates ABPA from invasive aspergillosis. The inflammatory response results in damage to the bronchial wall with airway destruction and the subsequent development of bronchiectasis. ABPA was initially described as a disease characterized by episodic wheezing, pulmonary infiltrates, pyrexia, sputum and blood eosinophilia, and sputum containing brown flecks or plugs. Almost all ABPA patients have clinical asthma. The disease may progress through various stages based on clinical, serologic, and radiographic findings. These stages need not occur in order. The first four stages—which are acute, remission, recurrent exacerbation, and corticosteroid-dependent asthma—are potentially reversible with no long-term sequelae. However, the fifth stage, fibrotic lung disease, in which bronchiectasis or fibrosis develops, is irreversible.[24]

***Aspergilloma or Saprophytic Aspergillosis.*** Aspergilloma is the most common form of pulmonary aspergillosis. It is noninvasive, involves the colonization of a preexisting pulmonary cavity or ectatic bronchus secondary to a wide variety of underlying pulmonary conditions, and occurs most often in the upper lobe. Simple aspergilloma develops in isolated thin-walled cysts lined by ciliated epithelium while the surrounding lung is normal. Complex aspergilloma develops in cavities formed by gross disease in the surrounding lung tissue. The most common underlying conditions are tuberculosis, sarcoidosis, and bronchiectasis. Histologically, the aspergilloma represents a fungal ball, or mycetoma, which consists of a mass-like conglomerate of intertwined hyphae intermingled with fibrin, cellular debris, mucus, and other blood products. This mycetoma may calcify in an amorphous or ring-like fashion. A pulmonary aspergilloma does not initiate the destructive pulmonary process, as is seen in ABPA and invasive aspergillosis. Most cases of aspergilloma are thought to arise from colonization and proliferation of the fungus in areas of devitalized lung with a poor blood supply. Most patients with pulmonary aspergilloma are asymptomatic. The most common presenting symptom, hemoptysis, has been reported in 50 to 80 percent of patients. Hemoptysis is usually intermittent and scanty but may be life-threatening. When symptoms such as cough, dyspnea, malaise, and weight loss are present, they are varied and are often difficult to ascribe to the aspergilloma in the presence of underlying pulmonary disease. Fever is an unusual finding in aspergilloma and suggests an alternate cause or concurrent bacterial infection.[25] Physical examination is generally nonspecific, although localizing signs such

as decreased air movement, bronchial breath sounds, and adventitial sounds may be heard.

***Invasive Pulmonary Aspergillosis.*** Invasive pulmonary aspergillosis (IPA) is now the most common fungal pulmonary infection in severely immunocompromised patients such as hematopoietic stem cell—or organ-transplant patients with hematologic malignancies undergoing intensive chemotherapy.[26] This infectious process is characterized by the invasion of blood vessels, resulting in multifocal infiltrates. Dissemination to other organs, particularly the CNS, may occur. Invasive aspergillosis typically manifests itself with fever, cough, sputum production, dyspnea, pleuritic chest pain, and sometimes hemoptysis in patients with prolonged neutropenia or immunosuppression. Fever that persists despite the administration of broad-spectrum antibiotics is present in a majority of patients except in corticosteroid-treated patients and is often the first clinical sign. Hypoxemia is present in diffuse disease. Among patients who have undergone organ transplantation, bone marrow recipients are most at risk for *Aspergillus* infection. In patients with leukemia and lymphoma, aspergillosis may occur after chemotherapy-induced bone marrow suppression, with resultant prolonged neutropenia.

## DIAGNOSIS

Several sets of diagnostic criteria incorporating the clinical, immunologic, and radiographic features of the disease have been proposed for the diagnosis of ABPA, since no single test is sufficiently discriminating. ABPA is defined by the following abnormalities: asthma, eosinophilia, a positive skin test result for *A. fumigatus*, marked elevation of the serum immunoglobulin E (IgE) level to greater than 1000 IU/dL, and positive test results for *Aspergillus* precipitins (primarily IgG, but also IgA and IgM antibodies). Chest x-ray characteristics include fleeting pulmonary infiltrates, central bronchiectasis, and mucoid impaction, which can result in lobulated masses or atelectasis. CT scanning is helpful in better defining bronchiectasis; images may show that the apparent lobulated masses are mucus-filled dilated bronchi. Minor criteria for diagnosis include positive *Aspergillus* radioallergosorbent assay test results, expectoration of brown plugs, and culture findings for *Aspergillus* in sputum. Histopathology and GMS staining may demonstrate degenerating eosinophils and typical fungal hyphae.

Aspergilloma does not cause many characteristic laboratory abnormalities. The diagnosis is usually made based on clinical and chest radiographic features coupled with serologic evidence of *Aspergillus* species. Results of the *Aspergillus* precipitin antibody test (i.e., for IgG) are usually positive. Chest radiography reveals a mass in a preexisting cavity, usually in an upper lobe, manifest by a crescent of air partially outlining a solid mass. Associated pleural thickening adjacent to the cavity is characteristic and may predate the development of an aspergilloma. CT scan images provide a better definition of the mass within a cavity and may demonstrate multiple aspergillomas in areas of extensive cavitary disease. Imaging can be performed with the patient in the supine and prone positions to demonstrate movement of the mass within the cavity.

Currently available antibody testing is not helpful for the diagnosis of invasive aspergillosis. In the appropriate clinical setting of pulmonary infiltrates in a patient who is neutropenic or immunosuppressed, visualization of the characteristic fungi, using silver stain or Calcofluor, or a positive culture result from sputum, needle biopsy, or BAL fluid should result in the prompt institution of therapy. Invasive aspergillosis demonstrates the characteristic septate hyphae, branching at acute angles, and acute inflammatory infiltrate and tissue necrosis with occasional granulomata and blood vessel invasion. A halo sign (i.e., an area of ground-glass infiltrate surrounding nodular densities on CT scan images) may be very helpful in the early diagnosis of aspergillosis. Later disease may show a crescent of air surrounding nodules, indicative of cavitation. Because *Aspergillus* is angioinvasive, infiltrates may be wedge-shaped, pleura-based, and cavitary, which is consistent with pulmonary infarction.

## MEDICAL TREATMENT

The goals of therapy for APBA are to treat acute exacerbations of disease and prevent the development of the fibrotic stage and bronchiectasis; therefore, early diagnosis is crucial. ABPA requires treatment with oral corticosteroids as a hypersensitivity reaction. Inhaled steroids are not effective. A recent double-blind, placebo-control trial has also demonstrated a potential benefit from the addition of oral itraconazole 200 mg twice daily to steroids. This may allow more rapid resolution of infiltrates and symptoms, facilitating steroid tapering or lowering the needed maintenance corticosteroid dosage. Bronchodilators such as β-agonists, anticholinergics, and leukotriene antagonists are also used for the treatment of asthma symptoms in ABPA.

Medical therapy is usually not effective for the treatment of aspergilloma because amphotericin B penetrates *Aspergillus* cavities poorly. Most patients are asymptomatic and treatment is not required unless significant hemoptysis occurs, in which case surgical intervention is indicated. Invasive aspergillosis is often rapidly progressive and has a high mortality rate; therefore, preventive therapy and rapid institution of therapy in patients in whom the diagnosis is suspected may be lifesaving. Prophylactic antifungal therapy with amphotericin B in high-risk patients may prevent invasive aspergillosis. The largest therapeutic experience is also with amphotericin B. Lipid formulations of amphotericin are indicated for the patient who has impaired renal function or who develops nephrotoxicity while receiving amphotericin. Oral itraconazole is an alternative for patients who can reliably take oral medication, especially those who respond to initial intravenous therapy.[27] Combination antifungal therapy sometimes may be used, or newer antifungal agents, such as caspofungin, may be instituted as monotherapy in patients in whom initial therapy with amphotericin B has failed.

Voriconazole is a new broad-spectrum triazole active in vitro against various yeasts and molds including *Aspergillus* species. A recent randomized trial showed that in patients with invasive aspergillosis, initial therapy with voriconazole led to better responses and improved survival and resulted in fewer severe side effects than the standard approach of initial therapy with amphotericin B.[28] For transplant patients, the level of immunosuppression should be decreased if possible.

### SURGICAL TREATMENT

Areas of mucoid impaction due to ABPA may have a mass-like appearance and are sometimes resected as an undiagnosed lung mass. Surgical removal of aspergilloma is definitive treatment; it has been advocated to be reserved for high-risk patients such as those with episodes of recurrent or life-threatening hemoptysis and patients who are immunocompromised. Aspergillomas tend to develop in clinically ill individuals with poor pulmonary function, and operations are often technically challenging because of the dense fibrosis around the cavity, the obliteration of pleural space and fissures, the enlarged and tortuous bronchial arteries, and the diseased pulmonary parenchyma surrounding the lesion. Inflammatory fibrosis of the pulmonary parenchyma and pleura may prevent the remaining lung from expanding fully so that it fills the pleural space after resection. For patients with life-threatening symptoms whose condition is unfit for pulmonary resection, cavernostomy and myoplasty may be considered.[29] Careful long-term follow-up is necessary in all patients because of the risk of recurrence. Overall, the morbidity of surgical treatment must be weighed against the clinical benefit for each patient. Bronchial artery embolization rarely produces a permanent success due to systemic collateral supply, but it may be useful as a temporizing procedure in patients with life-threatening hemoptysis. Other modalities that have been used include radiation therapy and endobronchial or percutaneous intracavitary instillation of amphotericin B under fluoroscopic or CT guidance. For invasive aspergillosis, the marginal response rates to antifungals, combined with the aggressive nature of the disease, lead to mortality rates that approach 90 percent with medical therapy alone, especially in immunocompromised patients. Aggressive surgical resection is therefore recommended for localized disease that has failed to respond to prolonged antifungal therapy.[30] A thoracoscopic approach has been reported that may result in a less-complicated postoperative course.[31]

## Coccidioidomycosis

### ETIOLOGY AND PATHOLOGY

Coccidioidomycosis is the infection caused by the dimorphic fungi of the genus *Coccidioides* (*C. immitis* and *C. posadasii*). These fungi are endemic to certain lower deserts of the southwestern United States. Infection is acquired by inhalation of a single arthroconidium, usually dust from uncultivated soil in the endemic areas. Within the lung, an arthroconidium changes from a barrel-shaped cell to a spherical structure and then greatly enlarges. Enlarging spherules produce internal septations; within each of the resulting subcompartments, individual cells (endospores) evolve. After several days, mature spherules rupture, releasing endospores into the infected tissue. If the infecting dose is huge or the person's immune status is impaired, overwhelming pulmonary disease and acute respiratory distress syndrome (ARDS) can occur. More often, localized pulmonary infection is the result. Coccidioidal pneumonia may clear, spread locally, or disseminate.

### CLINICAL PRESENTATION

Approximately two-thirds of infected persons experience few or no symptoms. The initial, or primary, infection is called valley fever when the disease is mild. Although the symptoms of coccidioidomycosis closely resemble those of other common respiratory infections, a respiratory illness with an accompanying rash in a patient with recent exposure to an endemic area is suggestive of a coccidioidal infection. Other systemic symptoms include fever, sore throat, malaise, and headache. Acute coccidioidal pneumonia may be self-limited or seems to respond to treatment with antibiotics. In certain situations, acute coccidioidal pneumonia may progress to involve the pleura, the formation of a mass-like lesion, necrosis, and cavity formation (coccidioidal cavities). In approximately 5 percent of patients, pneumonia can become chronic and cavities and nodules can persist as residual pulmonary nodules and chronic fibrocavitary pneumonia. The latter is characterized by night sweats, fatigue, weight loss, chronic cough, hemoptysis, and dyspnea. If necrosis involves the pleura, rupture with contamination of the pleura and extensive bronchopleural disease can ensue. When rupture does occur, a bronchopleural fistula is formed. Dyspnea and chest pain are the most common resulting symptoms, typical of a pneumothorax. Multiple areas of the lung may be involved due to seeding of several areas or airway spread of the infection.

Diffuse pulmonary or miliary coccidioidomycosis is the pulmonary manifestation of widespread dissemination in an individual with a very poor host response or if the fungal inoculum is large. The patient may manifest ARDS with hypoxia; in some cases, hypercapnea may also occur. *Coccidioides* may invade the vasculature, and spherules can be carried hematogenously to the entire pulmonary vasculature and many other organs. Extrapulmonary coccidioidomycosis can involve any organ; however, disseminated lesions are most commonly seen in the skin, lymph nodes, bones, and joints. Coccidioidal meningitis is also a manifestation of dissemination. Fortunately, disseminated disease occurs in only 0.5 to 1 percent of cases.[32]

### DIAGNOSIS

The clinical presentations of coccidioidomycosis are protean, necessitating a high index of suspicion for the disease.

A definitive diagnosis is established by the recovery of *Coccidioides* from respiratory secretions, tissues, or body fluids. Microscopic examination of sputum is positive in only 10 percent of cases. Bronchoscopy increases the yield dramatically, particularly if there is a lesion in the airways or parenchyma that can be biopsied. Alternatively, BAL is often useful. Respiratory samples should always be examined by cytology. Fine-needle aspiration of the lung often yields the organism, but more than one attempt is often necessary. Skin tests are not helpful in making the diagnosis. If skin lesions are present, a punch biopsy is quick and often positive. Pathologic examination using a silver stain shows granulomatous inflammation with the classic double-walled spherules with endospores. Serologic testing is one of the mainstays of diagnosis. The precipitin test, which measures IgM antibody, will be positive in 1 to 2 weeks and will remain positive for up to 6 months. Serology for the slower but more persistent IgG response is also tested using complement fixation or immunodiffusion assays and, more recently, enzyme immunoassay. Coccidioides will grow in nearly all laboratory media and often within the first week. The organism grows best at room temperature. A positive identification of the mold can be quickly made by a commercially available deoxyribonucleic acid (DNA) probe.

Radiographic manifestations vary depending on the clinical presentation. Residual coccidioidal cavities are commonly solitary and peripheral in location on a radiograph. Their walls are often strikingly thin with little or no discernible surrounding infiltrate. In ruptured cavities, an effusion coexists with the pneumothorax on chest x-ray, resulting in an air-fluid level. Since a spontaneous pneumothorax does not normally produce an effusion, this finding is of diagnostic significance. Chronic fibrocavitary pneumonia shows complex mixtures of infiltrate and cavitation. Hilar adenopathy is also common. A diffuse miliary or reticulonodular pattern on chest radiograph or CT scan (Fig. 6-5) is strongly associated with disseminated disease.[33] When disseminated disease is suspected, other diagnostic modalities include CT of the abdomen and pelvis and a bone scan to identify occult bony lesions. If the patient has even minimal CNS symptoms, an LP should be performed to rule out coccidioidal meningitis.

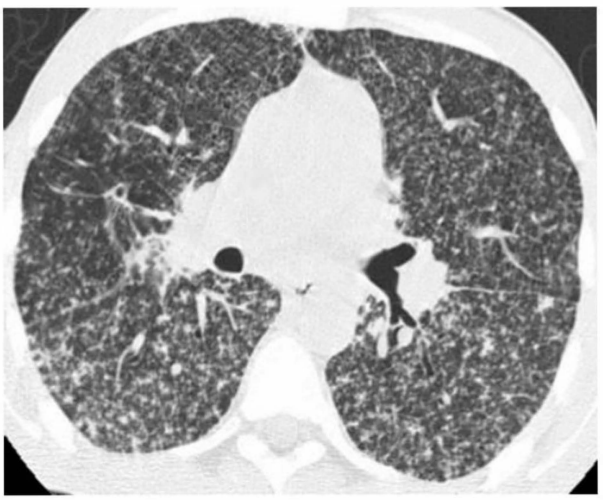


**FIGURE 6-5** Chest CT of a patient with miliary coccidioidomycosis.

## MEDICAL TREATMENT

In the absence of symptoms, treatment is not recommended. Since it is possible for coccidioidal cavities to change appearance, repeat chest radiographs at intervals ranging from 6 months to 2 years, depending on their apparent stability, are helpful in determining whether the lesion is enlarging or disappearing. Treatment is recommended if symptoms such as local pleural discomfort and hemoptysis occur. Such symptoms often improve after treatment with oral antifungal agents (ketoconazole, fluconazole, or itraconazole), but they may return if treatment is discontinued. The duration of treatment is typically 1 year or longer. A clinical response to treatment is usually evident by improvement in respiratory symptoms and periodic radiographs. Amphotericin B can be used for refractory infections unresponsive to oral therapy and is also the initial therapy of choice for rapidly progressive diffuse reticulonodular pneumonia and disseminated disease. As the patient's pulmonary status improves, treatment can be switched to an oral azole for at least 1 year. Patients with an underlying immunodeficiency state may have to be treated indefinitely.[34] A few case reports suggest that the new antifungal voriconazole is effective in disseminated disease refractory to other antifungals.[35]

## SURGICAL TREATMENT

Surgery is never the mainstay of treatment, although it may be critical for making the correct diagnosis. Cavities are considered candidates for resection if they are visible for longer than 2 to 4 years in association with symptoms, adjacent to pleura, rapidly enlarging, or thick walled or if they contain a fungus ball. Severe or recurrent hemoptysis is a strong indication for surgery. Surgical resection has also been recommended when the cavities occur in diabetic or pregnant patients and when they coexist with pulmonary tuberculosis.

In pyopneumothorax associated with a ruptured coccidioidal cavity, surgical resection of the cavity is the preferred approach if the condition is diagnosed promptly. If the diagnosis is delayed a week or more, a conservative approach with chest tube placement and oral antifungal treatment can be attempted. Persistent bronchopleural fistulas or lungs that are restricted by residual disease are other indications for surgery. In the case of ruptured cavities, the extent of surgical resection may have to be limited because of the extensive contamination of the pleural space. Lobectomy may not necessarily be indicated, since lesser resections are associated with equally low recurrence and complications rates.[36]

## Blastomycosis

### ETIOLOGY AND PATHOLOGY

North American blastomycosis is an endemic fungal infection predominantly seen in the south central and midwestern United States and portions of Canada. The disorder is the systemic pyogranulomatous disease caused by *B. dermatitidis*, a dimorphic organism usually acquired through inhalation of aerosolized conidia. At body temperature, these conidia transform to the yeast phase and a self-limited infection develops in the majority of persons. Rarely, blastomycosis may occur in accidental percutaneous exposure or following dog bites. Conjugal and perinatal transmissions have been reported, but person-to-person transmission is extremely rare. Most individuals who develop blastomycosis report occupations or hobbies—specifically hunting and fishing, camping, cutting timber, and operating heavy equipment—that likely enhance exposure to *B. dermatitidis*. The fungus has been identified in pigeon manure and soil. The major acquired host defense against *B. dermatitidis* is cellular immunity, which is mediated by antigen-specific T lymphocytes and lymphokine-activated macrophages. Chronic infection limited to the lungs or disseminated infection involving extrapulmonary sites develops in the minority of cases.

### CLINICAL PRESENTATION

Blastomycosis is a systemic disease that can involve virtually any organ. Acute blastomycosis is a condition that occurs with unknown frequency among patients exposed to *B. dermatitidis* through inhalation.[37] Most of the data from outbreaks suggest that the vast majority of patients exposed to *B. dermatitidis* develop a self-limited nonspecific flu-like illness that does not progress to chronic disease.

Chronic pulmonary blastomycosis is a disease usually manifest by symptoms of chronic pneumonia, which may progress to a pyogranulomatous process. Common symptoms include weight loss, fever, night sweats, and a cough productive of purulent sputum. Hemoptysis is uncommon. The disease is difficult to distinguish clinically from other fungal pulmonary diseases, tuberculosis, nocardiosis, chronic necrotizing bacterial pneumonia, and neoplastic disease. In fewer than 10 percent of cases, pulmonary blastomycosis presents with severe clinical manifestations, ARDS, and respiratory failure. This severe and unusual manifestation occurs in both immunocompromised and otherwise normal patients and is associated with an extremely high mortality. There are also several reports of so-called miliary blastomycosis associated with disseminated disease but not necessarily with frank respiratory failure. Many of these patients are severely immunosuppressed, but if a diagnosis is established early, there is often a favorable outcome with appropriate systemic antifungal therapy.

Extrapulmonary involvement with *B. dermatitidis* occurs in over 50 percent of patients with chronic blastomycosis. The skin and subcutaneous tissue are the most common sites. Typical lesions are verrucous (wart-like) plaques or cutaneous ulcers, frequently with a distinctive purplish hue surrounding the skin lesions. Subcutaneous disease is usually manifest as subcutaneous nodules that may suppurate and spontaneously drain, forming deep cutaneous ulcers. These lesions can easily be mistaken for pyoderma gangrenosum, squamous cell carcinoma, and other chronic cutaneous infections. Other sites that can be potentially involved include the genitourinary tract, bones, CNS, and the nasal and oral mucosa. Less common sites include the larynx, thyroid, sinuses, and eyes.

### DIAGNOSIS

The diagnosis of blastomycosis is established when *B. dermatitidis* is isolated from any clinical specimen. Transbronchial, transthoracic, or open-lung biopsy may be necessary. The organism grows well in the mycelial phase at 25°C to 30°C on routine fungal media. Conversion to the yeast phase at 37°C and demonstration of morphologically typical yeast forms confirms the identity of the organism. Commercial test kits are available that allow early identification of mycelial cultures by recognition of unique DNA sequences or fungus-specific exoantigens.[38] In culture-negative cases or before the culture becomes positive, the finding of broad-based budding yeast with a doubly refractile cell wall (Fig. 6-6) on histologic or cytologic specimens is strongly suggestive of *B. dermatitidis*. At present, there is no reliable, sensitive, and specific serologic methodology in use for routine diagnostic purposes.

Radiographically, chronic pulmonary blastomycosis does not have a typical appearance. Parenchymal abnormalities may occur in the upper lobes and may appear as unilateral or bilateral lobar or segmental abnormalities. Pulmonary nodules with or without cavitation and mass-like lesions are

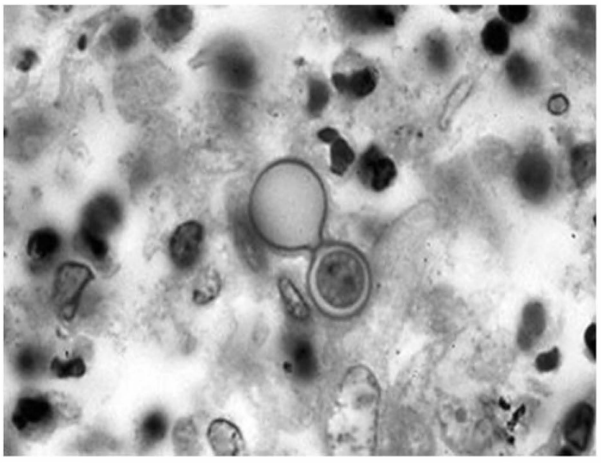


**FIGURE 6-6** Broad-based budding yeasts typical for *Blastomyces dermatitidis*.

frequently noted. The mass lesion of pulmonary blastomycosis may mimic carcinoma of the lungs. Pleural effusion and mediastinal lymphadenopathy may be seen in very few cases.

### MEDICAL TREATMENT

There is controversy as to whether patients with acute self-limited blastomycosis should be treated with antifungal therapy. Chronic blastomycosis, however, requires antifungal therapy because the disease rarely resolves spontaneously. Untreated, chronic blastomycosis can be associated with mortality rates approaching 60 percent. Most experts recommend a minimum of 6 months of oral azole (typically, itraconazole) therapy for mild-to-moderate pulmonary or nonmeningeal disseminated blastomycosis. The role of the amphotericin B formulations in the treatment of blastomycosis is probably limited to patients with severe or life-threatening disease, including all patients with CNS involvement, most immunocompromised patients (including transplant recipients and HIV-infected patients), and other iatrogenically immunosuppressed patients.[39] Amphotericin B is given as "induction therapy" to gain control of the disease, and an azole is given as "consolidation therapy" to complete at least 6 months of therapy. Long-term suppressive therapy may be needed in immunocompromised patients.

### SURGICAL TREATMENT

The main indication for surgery is usually to rule out malignancy. Surgical intervention is also necessary for drainage of large cavitary abscesses. Known blastomycotic cavitary lesions should be resected if they persist after adequate drug treatment. If the diagnosis is made only at the time of thoracotomy, drug treatment should follow operation.

## Cryptococcosis

*Cryptococcus neoformans* is an encapsulated yeast. The species has four serotypes based on antigenic specificity of the capsular polysaccharide; these include serotypes A and D (*C. neoformans var neoformans*) and serotypes B and C (*C. neoformans var gattii*). The *C. neoformans var neoformans* is the most common variety in the United States and other temperate climates throughout the world; it is found in aged pigeon droppings.[40] Naturally occurring cryptococcosis occurs in both animals and humans, but animal-to-human or person-to-person transmission via the pulmonary route has not been documented. Transmission via organ transplantation has been reported when infected donor organs were used. The lungs are thought to be the initial site of almost all infections due to *C. neoformans* and, after the CNS, they are the second-most clinically relevant site of infection. It is postulated that humans become infected with *C. neoformans* by inhaling the basidiospore form of this fungus. Basidiospores are smaller than the yeast forms obtained from clinical samples and have much smaller polysaccharide capsules, thus facilitating deposition in the alveoli and terminal bronchioles after inhalation. The alveolar macrophages ingest the yeast. Phagocytosis and destruction of the unencapsulated yeast cells readily occur, whereas encapsulated organisms are more resistant to phagocytosis. A cryptococcal polysaccharide capsule has antiphagocytic properties and may be immunosuppressive. Host response to cryptococcal infection includes both cellular and humoral components.

### CLINICAL PRESENTATION

The pattern of cryptococcal pulmonary disease is extremely variable, ranging from asymptomatic saprophytic airway colonization to ARDS, which is observed in hosts who are immunocompromised (e.g., patients with AIDS, organ transplant recipients). Subclinical primary infections are common and the vast majority of infected patients are asymptomatic. Symptoms may include cough with scant sputum, pleuritic chest pain, fever, weight loss, malaise, and rarely hemoptysis. Night sweats, as observed in tuberculosis, are uncommon in cryptococcal pulmonary disease but may occur with disseminated or CNS disease. On occasion, cryptococcal pulmonary disease may even manifest as a slowly progressive mass that can compress thoracic structures such as the vena cava. Although chronic infection can occur, patients who are immunocompetent normally have spontaneous regression of both clinical and radiologic manifestations. The presentation of pulmonary cryptococcosis in HIV-infected persons appears to be more acute and severe than in other patient groups. The severity of symptoms and extent of dissemination are inversely proportional to the CD4 lymphocyte count, with most symptomatic cases occurring in patients with counts less than 100/μL.[40]

*C. neoformans* infection is usually characterized by little or no necrosis or organ dysfunction until late in the disease. Organ damage may accelerate in persons with heavy infections. Organ damage stems primarily from tissue distortion secondary to the expanding fungal burden. Extensive inflammation or fibrosis is rare. The characteristic lesion consists of a cystic cluster of yeast with no well-defined inflammatory response. Well-formed granulomas generally are not present. After lung and CNS infection, the next most commonly involved organs in disseminated cryptococcosis are the skin, prostate, and medullary cavity of the bones.

### DIAGNOSIS

The diagnosis of active cryptococcal pulmonary infection can be suggested by the appearance of the characteristically encapsulated yeast forms in specimens of sputum, BAL fluid, or tissue. Culture of the organism from these same specimens can establish the diagnosis. *C. neoformans* is readily cultured in routine fungal medium that does not contain cycloheximide. In cases of clinically silent cryptococcal nodules that are sampled to rule out the possibility of malignancy, cultures of tissue can be negative despite the presence of yeast

on histopathologic inspection. Cultures of associated pleural effusion should be performed, as they are usually positive.

The use of the serum cryptococcal antigen as a screening test for pulmonary cryptococcosis is less likely to be positive in the immunocompetent population than in the immunocompromised. In fact, the test is positive in virtually all patients with HIV infection and pulmonary cryptococcosis. The presence of a positive serum cryptococcal antigen titer implies deep tissue invasion and a high likelihood of disseminated disease.[41] The testing of pleural fluid for the presence of the polysaccharide antigen can be very useful in suspected cases in which cultures are negative.

Radiographic manifestation features of pulmonary cryptococcosis in patients with pulmonary cryptococcosis vary widely. Well-defined, noncalcified nodules, either solitary or a few, are the most common radiographic findings. Cavitation in cryptococcal nodules is rare. Other possible findings in the chest include lobar infiltrates, masses, hilar and mediastinal adenopathy, and pleural effusions. An LP to obtain CSF for cryptococcal antigen testing and culture is indicated if the patient has neurologic symptoms or an underlying condition that predisposes to dissemination. An LP should also be strongly considered if the patient's serum cryptococcal antigen titer is very high (>1:250). CSF should also be tested if *Cryptococcus* is diagnosed from surgical specimen.

### MEDICAL TREATMENT

Patients with asymptomatic pulmonary cryptococcosis with a negative serum cryptococcal antigen may not require any systemic therapy. Patients presenting with symptomatic pulmonary infection should be treated with either fluconazole or amphotericin B. Fluconazole is preferred for most patients, since it can be administered orally and is less toxic than amphotericin B. Treatment with fluconazole should be continued for 36 months in immunocompetent patients. For those individuals who are unable to tolerate fluconazole, itraconazole for 6 to 12 months is an acceptable alternative. In the presence of more severe disease, treatment with amphotericin B may be necessary for 6 to 10 weeks. In immunocompromised patients, combination therapy with the amphotericin B and flucytosine is recommended, followed by high-dose fluconazole for a total of 10 weeks. After 10 weeks of therapy, the fluconazole dosage may be reduced, depending on the patient's clinical status.[41] It is recommended that all HIV-infected individuals continue maintenance therapy for life.

### SURGICAL TREATMENT

Surgical excision of infected pulmonary tissue is indicated only in cases of pseudotumor-like masses that impinge on adjacent structures. However, the diagnosis is often not clear until the time of surgical resection. Once the diagnosis is established, the lesion should not be resected unless it can easily be removed by wedge resection.[42] Pleural effusions can be treated with systemic therapy alone and rarely require drainage.

## Mucormycosis (Zygomycosis)

### ETIOLOGY AND PATHOLOGY

Mucormycosis refers to rare, severe infections with fungi of the order Mucorales. *Rhizopus* species are the most common causative organisms. They are saprophytic fungi that are ubiquitous in soil or decaying organic material. Spores produced by the fungi become airborne and are inhaled into the respiratory tract, which is the most common route of inoculation in a susceptible host. Humans with intact immunity are generally unaffected, but those with impairments of immunity due to cancer and its therapy, metabolic dysfunction (e.g., diabetes or ketoacidosis), or iatrogenic causes of immune suppression (e.g., steroids or cytotoxic chemotherapy) are at greatest risk for infection. Pulmonary and rhinocerebral infections predominate as a consequence of the frequency of airborne inoculation. Inhalation of spores in sawmill dust is also the source of allergic interstitial pneumonitis or alveolitis syndromes, which have been described in healthy lumber workers.

Direct contamination of skin or wounds by traumatic implantation of spores from soil and other environmental sources may occur, even in the hospital setting. Ingestion of spores with subsequent invasion of the gastrointestinal tract occurs rarely. Once spores reach tissue compartments, they germinate and hyphal elements develop and proliferate. The hyphal structures of the Zygomycetes are nonseptate or have rare septa, with broad, nonparallel walls. The hyphae are highly angioinvasive. Invasion of blood vessels by hyphae characteristically results in hemorrhage, thrombosis, infarction, and tissue necrosis. Death can result from progressive tissue destruction, uncontrolled hemorrhage, or both.

Pulmonary mucormycosis is a rapidly progressive infection that occurs when the spores settle in the bronchioles and alveoli. A diffuse pneumonia with infarction and necrosis results, and the infection can spread to contiguous structures such as the mediastinum and heart. Apparent hematogenous dissemination to the brain has also been described.

### CLINICAL PRESENTATION

Mucormycosis has a very high mortality rate of at least 50 percent. Due to the similarity in clinical features between mucormycosis and other more common filamentous fungal diseases and the difficulty in making a specific diagnosis, many cases of pulmonary mucormycosis are not suspected on the basis of clinical presentation. Neutropenic patients may present with fever refractory to broad-spectrum antibiotics, a cough that is typically nonproductive, severe or subtle pleuritic chest pain, and rapidly progressive dyspnea. Hemoptysis is a late sign indicating fungal erosion into blood vessels. Fatal hemoptysis due to fungal invasion of the pulmonary artery or aorta has occasionally been reported. If unchecked, the infection has a propensity to invade relentlessly through multiple tissue planes and erode into the chest wall, pericardium, myocardium, SVC, and diaphragm.

Obstruction of major airways by endobronchial masses due to fungi has been described in diabetic patients. Pulmonary involvement is often seen as a prelude to or in concert with disseminated zygomycosis. Once the disease has disseminated to other sites, including brain, skin, liver, or kidneys, the prognosis is poor. In patients with a mild degree of immune impairment, the pace of the disease is frequently less rapid. These patients may present with the slow development of cavitary lesions or pulmonary infiltrates or nodules in conjunction with fever and dry cough.

### DIAGNOSIS

The diagnosis of pulmonary mucormycosis can be difficult, since the presentation does not differ from that of diffuse pneumonias due to other microbial agents. There is a striking similarity to invasive aspergillosis. Sputum or BAL specimens can show the characteristic hyphae, which is usually the first clue to the presence of the disease. The hyphae can also be demonstrated on lung biopsy. A recent report of mucormycosis in cancer patients noted that about 80 percent with definite or probable pulmonary zygomycosis had a concomitant pneumonia due to another pathogen, either a mold (e.g., *Aspergillus* or *Fusarium*) or a bacterial species. Thus the presence of dual infection may obscure the diagnosis of mucormycosis. Accordingly, the detection of a Mucorales fungus in a respiratory sample should not be ignored, even if concomitant pathogens are also isolated in an immunosuppressed patient. Unfortunately, even when the correct diagnosis is made in a timely manner, the time between diagnosis and death is typically only a few days.

Radiographically, pulmonary mucormycosis may present as segmental or lobar infiltrates, isolated nodules, cavitary lesions, hemorrhage or infarction, or disseminated disease. A predilection for upper lobe involvement exists. Consolidation may be multilobar. Cavitation producing an air crescent is highly suggestive of fungal infection but does not distinguish mucormycosis from aspergillosis. Nodular lesions and pleural effusions may be present. When pulmonary mucormycosis is recognized, it should not be presumed to be isolated to that location. It is especially important to perform a CT scan of the sinuses and brain in the setting of pulmonary disease because these will be the most common sites associated with disseminated disease.[43]

### MEDICAL TREATMENT

Early diagnosis and correction of the underlying abnormality such as control of diabetes and prompt institution of amphotericin B therapy is critical to survival. Neutropenia in association with hematologic malignancy and its treatment should be reversed, if possible, with the use of colony-stimulating factors and the withdrawal of cytotoxic chemotherapy. Attempts should be made to wean glucocorticosteroids and other immunosuppressive drugs. There is no role for flucytosine or the currently available azole antifungals in the therapy of this infection.

### SURGICAL TREATMENT

Most patients present with multilobar involvement, which may preclude surgical resection. When feasible, extensive surgical debridement of as much involved tissue as possible is necessary. Amphotericin B is used as adjunctive therapy after aggressive surgical debridement. There are reports of patients with early pulmonary infection who were cured with lobectomies.[44]

## Candidiasis (Moniliasis)

### ETIOLOGY AND PATHOLOGY

*Candida* species are ubiquitous fungi and are the most common fungal pathogens affecting humans. They are yeast-like fungi that can form true hyphae and pseudohyphae. The genus *Candida* encompasses more than 160 species. The most common of these are *Candida albicans, Candida krusei, Candida parapsilosis, Candida tropicalis,* and *Candida glabrata*. For the most part, *Candida* species are confined to human and animal reservoirs; however, they are frequently recovered from the hospital environment, including on foods, countertops, air-conditioning vents, floors, respirators, and medical personnel. Although *Candida* are considered normal flora in the gastrointestinal and genitourinary tracts of humans, they have the propensity to invade and cause disease when an imbalance is created in the ecologic niche in which these organisms usually exist. The growing problem of mucosal and systemic candidiasis reflects the enormous increase in the pool of patients at risk and the increased opportunity that exists for *Candida* species to invade tissues normally resistant to invasion. *Candida* species are true opportunistic pathogens that exploit recent technologic advances to gain access to the circulation and deep tissues. Thus, needles, IV cannulas, or urinary bladder catheters are examples of the portals of infection.

### CLINICAL PRESENTATION

The clinical manifestations of infection with *Candida* species range from local mucous membrane infections to widespread dissemination with multiorgan system failure. Pneumonia due to *Candida* is poorly defined as a clinical entity because positive cultures cannot distinguish between true infection and either colonization or contamination of samples with oropharyngeal contents.[45] In addition, the presence of clinical pneumonia may be due to coinfecting pathogens. Much more commonly, the lungs are one of many organs involved in the course of disseminated infection with *Candida* in immunosuppressed patients. The only criterion for the definitive diagnosis of candidal pneumonia was the histologic demonstration of fungus in lung tissue. In addition to the rare candidal pneumonia, other special clinical situations encountered by the thoracic surgeon in candidiasis include esophagitis and endocarditis.

### DIAGNOSIS

Species of *Candida* are present in 50 to 60 percent of respiratory secretions drawn from uninfected individuals. The presence of the fungi in bronchial or lung biopsies, in blood or deep tissue spaces is more likely due to invasive infection, especially in the immunocompromised host. This is particularly true for CSF culture, which is normally sterile. No reliable serologic test is available. Nonspecific patchy infiltrates may be noted on radiographic imaging.

### MEDICAL TREATMENT

If feasible, initial management should include removal of all existing portals such as central venous catheters. Management of serious and life-threatening invasive candidiasis remains severely hampered by delays in diagnosis and the lack of reliable diagnostic methods that allow for the detection of both fungemia and tissue invasion by *Candida* species.

Whenever possible, initiation of treatment for isolated candidal pneumonia should be based on histologic evidence in the nonneutropenic host. Most patients with isolated candidal pneumonia have been treated with conventional amphotericin B. In contrast, patients with hematogenously disseminated infection who develop secondary candidal pneumonia should be treated for disseminated disease rather than candidal pneumonia alone. In this case, initial medical therapy should involve caspofungin, fluconazole, an amphotericin B preparation, or combination therapy with fluconazole plus amphotericin B.

### SURGICAL TREATMENT

Surgical intervention is rarely indicated except for the occasional development of lung abscess and need for repair or replacement of valves due to candidal endocarditis.

## Sporotrichosis

### ETIOLOGY AND PATHOLOGY

Sporotrichosis is a subacute to chronic infection caused by the dimorphic fungus *Sporothrix schenckii,* which is found throughout the world in decaying vegetation, sphagnum moss, and soil. *S. schenckii* exhibits thermal dimorphism. It produces hyphae in the environment at temperatures that are lower than normal human body temperatures; in comparison, it exists as a yeast form when at 37°C in human tissues. The hyphae are rather thin and septate, showing branching and stranding. The characteristic infection involves suppurating subcutaneous granulomas that progress proximally along lymphatic channels (lymphocutaneous sporotrichosis). Other tissues are involved by direct extension and, less often, by hematogenous dissemination. The most common extracutaneous sites are in the bones, joints, tendon sheaths, and bursae.

Pulmonary sporotrichosis is a rare form that appears to result from inhalation of the organism from soil. Most patients have been involved in an occupation that exposes them to aerosols from soil, but discrete point sources have rarely been identified. A chronic cavitary pneumonia, which is clinically and radiographically indistinguishable from tuberculosis and histoplasmosis, occurs in patients who usually have severe underlying COPD. Rarely, a disseminated infection occurs with disseminated cutaneous lesions and involvement of multiple visceral organs, including meningitis; this occurs most commonly in patients with AIDS.

### CLINICAL PRESENTATION

Symptoms mimic those of tuberculosis, including constitutional complaints of fever, night sweats, weight loss, and fatigue as well as respiratory complaints including dyspnea, cough, purulent sputum, and hemoptysis. The typical patient is a Caucasian, middle-aged male who often smokes and abuses alcohol and may have underlying COPD. Physical examination of patients with pulmonary sporotrichosis is dominated by the findings of the underlying COPD.

The major differential diagnoses include tuberculosis; chronic fungal infections, especially histoplasmosis; and sarcoidosis. Some patients with pulmonary involvement have evidence of dissemination to skin, osteoarticular structures, or viscera. Almost without exception, untreated pulmonary sporotrichosis progresses to death.

### DIAGNOSIS

Culture is the "gold standard" for establishing a diagnosis of sporotrichosis and is also the most sensitive method. Aspirated material from a lesion, sample from a tissue biopsy, sputum, or body fluids should be inoculated onto Sabouraud medium or blood agar and incubated at room temperature. Incubation at this temperature facilitates growth of the mycelial phase of *S. schenckii,* with the characteristic arrangement of conidia on the hyphae. Occasionally, the organism (cigar-shaped yeast) can be visualized in biopsied tissue specimens that are stained with PAS, Gomori methenamine-silver, or immunohistochemical stains. Sporotrichosis is characterized histopathologically by a mixed granulomatous and pyogenic process with occasional asteroid bodies. Asteroid bodies consist of a central basophilic yeast surrounded by eosinophilic material radiating outward like spokes on a wheel, probably representing antigen–antibody complexes. Although previously thought to be specific for sporotrichosis, this tissue reaction can be seen in other fungal infections as well.

Serology is less useful in the diagnosis of sporotrichosis than in other endemic mycoses. The radiographic findings are also nonspecific and similar to those of tuberculosis.

### MEDICAL TREATMENT

Pulmonary sporotrichosis is difficult to treat, perhaps due to delayed diagnosis or the underlying illnesses in infected

patients. If the patient is seriously ill, amphotericin B should be used initially; if not, then itraconazole can be given. Another option is to begin therapy with amphotericin B and, when the patient is stable, switch to itraconazole. The duration of azole therapy should be at least 1 year, perhaps longer in some patient.[46]

### SURGICAL TREATMENT

The most effective therapy for pulmonary sporotrichosis appears to be a combination of amphotericin B and subsequent surgical resection. However, many patients are unable to tolerate such a procedure because of severe underlying pulmonary disease. Surgical resection is particularly useful for those patients who have focal lesions.

## TUBERCULOSIS AND ATYPICAL MYCOBACTERIAL DISEASES

### Tuberculosis

### ETIOLOGY AND PATHOLOGY

Tuberculosis (TB) is an infectious disease that has plagued humans since the neolithic era. After decades of declining incidence in the United States, an unprecedented resurgence in TB occurred in the late 1980s and early 1990s. Deterioration of the TB program infrastructure, the HIV/AIDS epidemic, drug-resistant TB, and, less so, TB among foreign-born persons contributed to the resurgence. Worldwide, TB continues to be a major health problem. There were an estimated 8.3 million new TB cases in 2000 and an estimated 1.8 million deaths from TB. TB is still on the top 10 list for all-cause, all-age worldwide mortality.[47]

Due to novel genetic markers, there are now five closely related mycobacteria grouped in the *M. tuberculosis* complex: *M. tuberculosis, Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti,* and *Mycobacterium canetti. M. tuberculosis* is transmitted through the airborne route and there are no known animal reservoirs. *M. bovis* may penetrate the gastrointestinal mucosa or invade the lymphatic tissue of the oropharynx when ingested in milk containing large numbers of organisms. Human infection with *M. bovis* has decreased significantly in developed countries as a result of the pasteurization of milk and effective TB control programs for cattle. Airborne transmission of both *M. bovis* and *M. africanum* can also occur.

*M. tuberculosis* is a rod-shaped, slow-growing bacterium. Its cell wall has high acid content, which makes it hydrophobic or resistant to oral fluids. The cell wall absorbs a certain dye and maintains a red color despite attempts at decolorization, hence the name acid-fast bacillus. TB is spread from person to person through the air by droplet nuclei, particles 1 to 5 μm in diameter that contain *M. tuberculosis* complex. A single cough can generate 3000 infective droplets. They may also be produced by aerosol treatments, sputum induction, aerosolization during bronchoscopy, and through manipulation of lesions or processing of tissue or secretions in the hospital or laboratory. Droplet nuclei, containing two to three *M. tuberculosis* organisms, are so small that air currents normally present in any indoor space can keep them airborne for long periods of time. Droplet nuclei are small enough to reach the alveoli within the lungs, where the organisms replicate. Four factors determine the likelihood of transmission of *M. tuberculosis*: (1) the number of organisms being expelled into the air, (2) the concentration of organisms in the air as determined by the volume of the space and its ventilation, (3) the length of time an exposed person breathes the contaminated air, and (4) presumably the immune status of the exposed individual.

After inhalation, the droplet nucleus is carried down the bronchial tree and implants in a respiratory bronchiole or alveolus. Whether or not an inhaled tubercle bacillus establishes an infection in the lung depends on both the bacterial virulence and the inherent microbicidal ability of the alveolar macrophage that ingests it. *M. tuberculosis* has no known endotoxins or exotoxins; therefore, there is no immediate host response to infection. The organisms grow for 2 to 12 weeks, until they reach $10^3$ to $10^4$ in number, which is sufficient to elicit a cellular immune response that can be detected by a reaction to the tuberculin skin test. Before the development of cellular immunity, tubercle bacilli spread via the lymphatics to the hilar lymph nodes and thence through the bloodstream to more distant sites.

In persons with intact cell-mediated immunity, collections of activated T cells and macrophages form granulomas that limit multiplication and spread of the organism. Antibodies against *M. tuberculosis* are formed but do not appear to be protective. The organisms tend to be localized in the center of the granuloma, which is often necrotic. For the majority of individuals with normal immune function, the proliferation of *M. tuberculosis* is arrested once cell-mediated immunity develops, even though small numbers of viable bacilli may remain within the granuloma. It is estimated that approximately 10 percent of individuals who acquire TB infection and are not given preventive therapy will develop active TB. The risk is highest in the first 2 years after infection, when half the cases will occur. The ability of the host to respond to the organism may be reduced by certain diseases such as silicosis, diabetes mellitus, and diseases associated with immunosuppression (e.g., HIV infection) as well as by corticosteroids and other immunosuppressive drugs.

### CLINICAL PRESENTATION

TB inoculation can result in latent infection or active disease. Depending on the population, 10 to 30 percent of inoculated individuals progress directly to active primary disease. More commonly, however, TB inoculation results in an asymptomatic latent infection. Purified protein derivative (PPD) skin test conversion and identification of a Ghon complex (characterized by a peripheral lesion with associated hilar

adenopathy) on chest radiography are the only means of identifying such cases. Patients often remain healthy for years; however, some experience reactivation of their disease due to subsequent immunologic stressors. Reactivated TB represents 90 percent of adult cases in the non-HIV-infected population and results from reactivation of a previously dormant focus seeded at the time of the primary infection. The apical posterior segments of the lung are frequently involved. Such reactivation occurs at a rate of approximately 1 percent per year in immunocompetent hosts. In immunocompromised hosts, the conversion rate increases to 10 percent. Roughly 80 percent of TB cases involve pulmonary disease, although TB can involve any organ system. In patients who are severely immunocompromised, extrapulmonary disease and atypical presentations are common.

Cough is the most common symptom of pulmonary TB. Early in the course of the illness it may be nonproductive, but subsequently, as inflammation and tissue necrosis ensue, sputum is usually produced and is key to most diagnostic methods. Fever, night sweats, anorexia, and weight loss are other classic symptoms. Hemoptysis may rarely be a presenting symptom but is usually the result of previous disease and does not necessarily indicate active TB. Hemoptysis may result from residual tuberculous bronchiectasis, caseous sloughing or endobronchial erosion, rupture of a dilated vessel in the wall of a cavity (Rasmussen's aneurysm), bacterial or fungal infection (especially *Aspergillus* in the form of a mycetoma) in a residual cavity, or erosion of calcified lesions into the lumen of an airway (broncholithiasis). Inflammation of the lung parenchyma adjacent to a pleural surface may cause pleuritic pain. Dyspnea can occur when patients have extensive parenchymal involvement, pleural effusions, or a pneumothorax. Overall, the symptoms in reactivated TB typically begin insidiously and are present for weeks or months before the diagnosis is made. It is noteworthy that classic symptoms are usually absent, especially in the elderly and immunocompromised patients. Rales may be heard in the area of involvement, as well as bronchial breath sounds if there is lung consolidation. Other nonspecific findings include cachexia, hypoxia, tachycardia, and lymphadenopathy.

## DIAGNOSIS

Early identification and diagnosis of cases of active TB is key to the effectiveness of control programs. However, maintaining a high index of suspicion for TB is crucial, and diagnostic testing remains problematic. Culture of appropriate specimens for isolation of *M. tuberculosis* and susceptibility testing is the cornerstone for a diagnosis of TB, but the organism still requires weeks to grow in culture.

Pulmonary TB is diagnosed by visualization of acid-fast bacilli on a sputum smear and isolation of the organism from a culture of this sputum. Most laboratories use auramine–rhodamine or auramine O to stain the sputum, allowing scanning for fluorescence as opposed to Ziehl–Neelsen stain, which requires more time and labor to identify organisms.[48] Both concentrating sputum specimens and obtaining a larger quantity of sputum (5 mL) have been shown to increase the probability of visualizing organisms by smear. The conventional teaching is that sputum specimens should be obtained on 3 consecutive days and that first morning specimens have the highest yield. If the patient has difficulty producing sputum, inhalation of an aerosol of sterile hypertonic saline, usually produced by an ultrasonic nebulizer, can be used to stimulate the production of sputum. Multiple samples increase the diagnostic yield of the test. For patients in whom a diagnosis of TB has not been established from sputum, fiberoptic bronchoscopy performed with appropriate infection control precautions may be needed with BAL. Gastric aspirates obtained in the morning can also be cultured for *M. tuberculosis* and reflect sputum swallowed over the course of the night. It is helpful in patients who cannot produce enough sputum even with induction, especially children. The disadvantage is that AFB smears cannot be done on gastric aspirates. Urine, blood, CSF, and other body fluids can also be obtained for culture. Invasive procedures to obtain specimens from the lung, pericardium, lymph nodes, and so on should be considered when noninvasive techniques do not provide a diagnosis. Many of these areas are amenable to closed techniques such as percutaneous needle biopsy or aspiration, transbronchial biopsy, or brushing, precluding a need for formal surgical procedures. In patients with hematogenous or disseminated disease, bone marrow biopsy, lung biopsy, and liver biopsy for histologic examination and culture should be considered. Appropriate measures must be taken in collecting these specimens to minimize aerosolation of *M. tuberculosis* organisms and prevent transmission of infection to personnel. Maintenance of laboratory proficiency requires continuing and frequent performance of the required tests. Adequate training in proper techniques and the availability of special containment areas are required for the safe manipulation of clinical specimens.

The tuberculin test is based on the fact that infection with *M. tuberculosis* produces a delayed-type hypersensitivity reaction to certain antigenic components of the organism that are contained in extracts of culture filtrates or "tuberculins." Tuberculin skin testing using 5 units (0.1 mL) of PPD injected intradermally (Mantoux method), usually into the volar or dorsal surface of the forearm, may be used for screening or to supplement other diagnostic testing. Induration, not erythema, is measured 48 to 72 h after injection. Tests read after 72 h tend to underestimate the true size of induration. On the basis of the sensitivity, specificity, and the prevalence of TB in different groups, three cut points have been recommended for defining a positive tuberculin reaction (Table 6-1).[48] Overall, skin testing for TB serves mainly as an epidemiologic tool to assess exposures. Patients with positive reactions may not have active TB, and 20 to 30 percent of those with a new diagnosis of active TB have negative reactions, particularly those with advanced disease.[49] Testing is also unreliable in infants, patients with immunosuppressive conditions, and those with serious illnesses. There is no reliable method of distinguishing tuberculin reactions caused by vaccination with bacillus Calmette–Guérin (BCG) from

**TABLE 6-1: Guidelines for Determining a Positive Tuberculin Skin Test Reaction[a]**

| Induration ≥5 mm | Induration ≥10 mm | Induration ≥15 mm |
|---|---|---|
| HIV-positive persons | Recent arrivals (<5 years) from high-prevalence countries | Persons with no risk factors for TB |
| Recent contacts of TB case | Injection drug users<br>Residents and employees[a] of high-risk congregate settings: prisons and jails, nursing homes and other health-care facilities, residential facilities for AIDS patients, and homeless shelters, mycobacteriology laboratory personnel | — |
| Fibrotic changes on chest radiograph consistent with old TB | Persons with clinical conditions that place them at high risk: silicosis diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of >10% of ideal body weight, gastrectomy, jejunoileal bypass | — |
| Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of >15 mg/day prednisone for >1 month) | Children <4 years of age or infants, children, and adolescents exposed to adults in high-risk categories | — |

[a]For persons who are otherwise at low risk and are tested at entry into employment, a reaction of >15 mm induration is considered positive.

*Source:* From the American Thoracic Society and the Centers for Disease Control and Prevention, 2000.[48] With permission.

those caused by natural mycobacterial infections. It is usually prudent to consider "positive" reactions to 5 tuberculin units of PPD in BCG-vaccinated persons as indicating infection with *M. tuberculosis*. Because most persons who have received BCG are from high-prevalence areas of the world, it is important that vaccinated persons who have a positive reaction to a tuberculin skin test be evaluated for TB and treated accordingly.

Nucleic acid amplification tests, such as the polymerase chain reaction (PCR) and other methods for amplifying DNA and RNA, may facilitate rapid detection of microorganisms. Both RNA and DNA amplification systems are commercially available. In clinical respiratory specimens that are AFB smear-positive, the sensitivity of the amplification methods is approximately 95 percent, with a specificity of 98 percent. In specimens that contain fewer organisms and are AFB smear-negative, the nucleic acid amplification test is positive in 48 to 53 percent of patients with culture-positive TB and the specificity remains approximately 95 percent. Thus, the CDC includes a positive nucleic acid amplification test in the setting of a positive smear as confirmation of the diagnosis of TB.[50]

Radiographic findings in TB depend on the stage of the infection. Primary pulmonary TB (primary exposure) is characterized by the Ghon complex and consists of (1) a subpleural (fissure) focus of inflammation and (2) infected (inflamed) lymph nodes draining the primary subpleural lesion, which manifests as ipsilateral hilar adenopathy (Fig. 6-7). Atelectasis may result from the compression of airways by enlarged lymph nodes. Overall, intrathoracic adenopathy is less common in immunocompetent adults than in children and immunosuppressed patients. Cavitation may occur in progressive primary TB if the process persists beyond the time when specific cell-mediated immunity develops and is more common in reactivation (secondary)

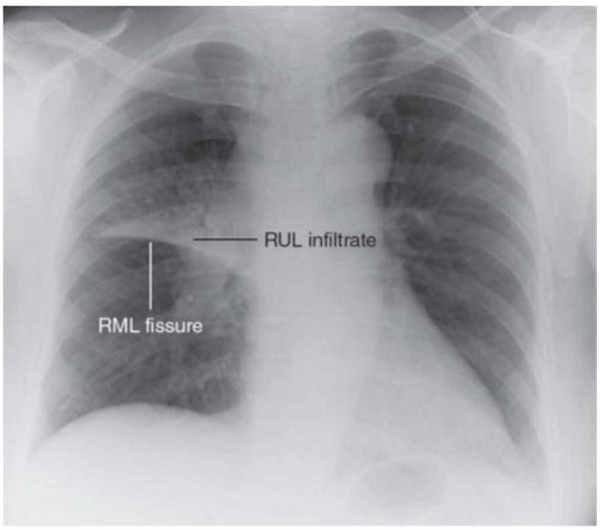



**FIGURE 6-7** Posteroanterior chest x-ray of a patient with tuberculosis. The combination of right-upper-lobe infiltrate and hilar adenopathy should raise suspicion of tuberculosis as the potential infectious agent. RML, right middle lobe; RUL, right upper lobe.



FIGURE 6-8 Chest x-ray of a patient with miliary tuberculosis.

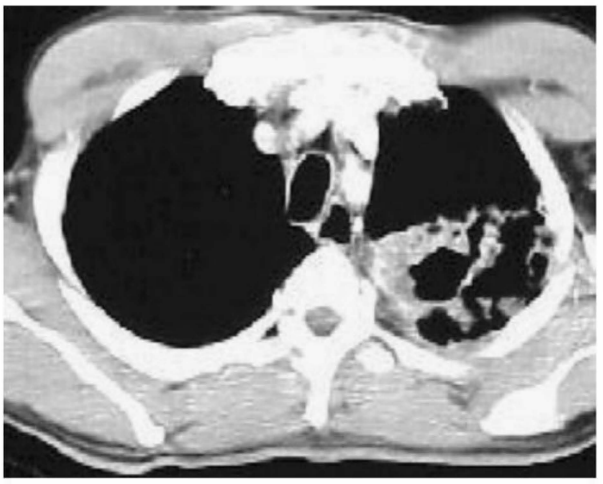


FIGURE 6-9 Chest CT of a patient with cavitary pulmonary tuberculosis involving the left upper lung.

TB. In this form, the most frequent sites of abnormalities are the apical and posterior segments of the right upper lobe and the apical-posterior segment of the left upper lobe. These lesions correspond pathologically with caseating granulomas. Miliary TB results from erosion of a parenchymal focus of TB into the blood or lymph vessel, leading to dissemination of the organism. This results in evenly distributed small nodules on chest film (Fig. 6-8). Healing of the tuberculous lesions usually results in the development of fibrosis with loss of lung parenchymal volume and, often, calcification. Nodules and fibrotic lesions of old healed TB have well-demarcated, sharp margins and are often described as "hard." Old TB can also cause pleural scarring. Bronchiectasis of the upper lobes is a nonspecific finding that sometimes occurs from previous pulmonary TB.

Notably, patients with endobronchial lesions and those who are immunosuppressed may have no associated abnormalities on chest x-ray. In patients with HIV infection, the nature of the radiographic findings depends to a certain extent on the degree of immunocompromise produced by the HIV infection. TB that occurs relatively early in the course of HIV infection tends to have the typical radiographic findings described above. With more advanced HIV disease, the radiographic findings become more "atypical": Cavitation is uncommon, and lower-lung-zone or diffuse infiltrates and intrathoracic adenopathy are frequent.[51]

CT scanning is more sensitive than plain chest radiography for diagnosis, particularly for smaller lesions located in the apex of the lung. CT scan may show a cavity (Fig. 6-9), centrilobular lesions, nodules, and branching linear densities sometimes called a "tree in bud" appearance.

## MEDICAL TREATMENT

The overall goals for treatment of TB are (1) to cure the individual patient and (2) to minimize the transmission of *M. tuberculosis* to other persons. It is necessary to isolate any patient with suspected TB infection in a private room with negative pressure. Anyone entering should wear high-efficiency disposable masks sufficient to filter the TB bacillus. Isolation should be continued until sputum smears return negative results three consecutive times. Such sterilization usually requires 2 to 4 weeks of treatment and must be accompanied by clinical improvement.

There are currently four broadly applicable recommended regimens for treating patients with TB caused by drug-susceptible organisms. Each regimen has an initial phase of 2 months followed by a choice of several options for the continuation phase of either 4 or 7 months. The initial phase is usually composed of different three- or four-drug combinations of isoniazid, rifampin, ethambutol, and pyrazinamide. The continuation phase is usually a combination of isoniazid and rifampin or rifapentin. Rifapentin is a rifampin with an increased half-life and enhanced activity against *M. tuberculosis*. Complete information can be found in the 2003 statement from the American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America (IDSA) on the treatment of TB.[52] This document contains details of specific drug therapy, including suggestions relating to monitoring for adequate response to therapy and details of monitoring for drug toxicity. Special treatment situations, including HIV infection, TB in children, extrapulmonary TB, culture-negative TB, pregnancy and breast-feeding, hepatic disease, and renal disease are discussed in detail. The use of less commonly employed antituberculous drugs for multidrug-resistant TB is also discussed.

## SURGICAL TREATMENT

Surgery has largely been supplanted by medical therapy for the treatment of pulmonary TB infection. This resulted

mainly from the introduction of effective antibiotics in the 1960s. With the emergence of multidrug-resistant TB (MDR-TB), surgery is again becoming a necessary treatment modality. In destroyed lungs, cavitary disease, and patients with advanced disease, medications are often unable to penetrate the lesions. In the setting of such permanent anatomic changes, medical therapy alone has a very high failure rate; the addition of surgery with removal of the nidus of infection improves the cure rate.[53]

Contemporary indications for surgery in patients infected with *M. tuberculosis* include:

- Surgery for diagnosis of pulmonary lesions or mediastinal adenopathy of unknown etiology
- Highly resistant *M. tuberculosis* with localized disease
- Persistent cavitary disease especially with Aspergillus colonization
- Continued sputum positivity especially in the setting of MDR-TB
- Destroyed lobe or lung (lung gangrene)
- Massive hemoptysis
- Bronchopleural fistula with failed tube thoracostomy
- Bronchial stenosis
- Complications resulting from previous or insufficient surgery (e.g., delayed complications of plombage)

Excisions (segmentectomies, lobectomies, and pneumonectomies) currently represent the majority of operations, followed by operations on the pleura (decortication) and rarely those on the thoracic wall (thoracoplasty). The basic principles remain unchanged: best available drug therapy, followed by complete resection of residual active foci of disease, accompanied by obliteration of abnormal pleural spaces using muscle/omental flaps, followed by best available drug therapy for 12 to 24 months.

Appropriate preoperative preparation of these patients is important. When feasible, attempts should be made to convert the patient's sputum to negative. Except in cases of emergency, such as massive hemoptysis, patients should receive at least 3 months of therapy prior to surgical consideration. Pulmonary function tests should be performed to assess the feasibility of resection, as well as CT scan of the chest to determine the extent of involvement of the lungs by the disease and to evaluate anatomic changes. Ventilation/perfusion scanning provides the important information about the amount of viable lung; if only 15 percent or less of lung tissue will remain after resection, then pneumonectomy of that lung is indicated. The nutritional status of the patient and pulmonary hygiene should also be improved prior to surgery. Bronchoscopy is essential to evaluate for tuberculous endobronchial disease and help avoid the serious postoperative complication of bronchopleural fistula. This is more likely to occur when bronchial closure encompasses an area involved by tuberculous bronchitis.

Pomerantz et al.[54] recently reported a large series of pulmonary resection for MDR-TB. During a 17-year period, 172 patients underwent 180 pulmonary resections, which included 98 lobectomies and 82 pneumonectomies, with an acceptable operative mortality of 3.3 percent; late mortality was 6.8 percent. Significant morbidity was 12 percent. Muscle flaps were frequently used to avoid residual space and bronchial stump problems. The authors concluded that surgery remains an important adjunct to medical therapy for the treatment of MDR-TB. In the setting of localized disease, persistent sputum positivity, or patient intolerance of medical therapy, pulmonary resection should be undertaken.

## Atypical Mycobacterial Infections

There is continued growth in the number and prevalence of mycobacteria species other than the *M. tuberculosis* complex and are collectively referred to as the nontuberculous mycobacteria (NTM).[55] The most common cause of NTM pulmonary disease is *Mycobacterium avium* complex (*M. avium* and *Mycobacterium intracellulare*), known as MAC complex, *Mycobacterium kansasii, Mycobacterium abscessus,* and *Mycobacterium fortuitum*. Other NTM (e.g., *Mycobacterium malmoence, Mycobacterium simiae, Mycobacterium szulgai,* and *Mycobacterium xenopi*) have been identified as causative agents of this disease with much lesser frequency. *M. kansasii* is the most common atypical mycobacterium in the Central United States, whereas MAC is the most common in the South and Southeast. NTM disease is not reportable in the United States; therefore, reliable estimates of its incidence or prevalence have been limited. A CDC study from 1991 to 1992, which included results from 33 state laboratories, demonstrated that there were more isolates of *M. avium* complex than *M. tuberculosis*, with the latter representing only 26 percent of the total mycobacterial isolates. The reasons for this dramatic increase in numbers for NTM is unknown, but better clinical recognition and more culturing for both pulmonary and disseminated disease are felt to play important roles. It is well documented that the reservoir for most of these infections is soil, natural waters, and aerosols created from these sources. Epidemiologic studies, skin test surveys, and, more recently, DNA fingerprinting studies suggest that person-to-person transmission of infection is rare. It is assumed that most persons are infected from environmental sources, by airborne mechanisms (especially in respiratory disease), and, for some situations, possibly via the gastrointestinal route.

Infections caused by NTM may take place without any obvious predisposing conditions. Coexisting medical conditions that increase the risk for developing an infection include HIV/AIDS, cystic fibrosis, diabetes mellitus, malignancy, dialysis, tissue/organ transplant, smoking, COPD, bronchiectasis, silicosis and other pneumoconiosis, and previous TB. There is higher prevalence of NTM infections in warm climate regions, with high rates among miners. Demographically, females in the sixth decade of life or later are considered the most vulnerable to NTM infections, especially pulmonary infection with *M. avium*.

## CLINICAL MANIFESTATIONS

The clinical manifestation of NTM, especially in HIV-negative patients, can be very similar to those of TB. They include chronic cough, sputum production, and fatigue. Less commonly, malaise, dyspnea, fever, hemoptysis, and weight loss can also occur, usually with advanced NTM disease. Pulmonary disease due to *M. avium* complex in HIV-negative patients may have two types of presentations, as clarified in the recent American Thoracic Society (ATS) statement.[55] One is an apical fibrocavitary disease that has a tendency to progress within 1 to 2 years if the patient does not receive antimicrobial therapy. The other type is a bilateral or isolated right middle lobe/lingular nodular and interstitial/nodular disease, with a much slower progression within a period of 5 to 10 years. In addition, some authors identify "atypical manifestations" of this disease; namely, the combination of bronchiectasis and small nodules (so-called Lady Windermere syndrome) and focal mass-like opacities. In immunocompromised patients, specifically AIDS patients, MAC is the most common bacterial complication. Disseminated disease is frequent, with manifestations such as hepatomegaly, diarrhea, splenomegaly, and abdominal pain.

*M. kansasii* causes lung disease that is clinically indistinguishable from TB. Symptoms may be less severe and more chronic compared to infection with *M. tuberculosis*. Asymptomatic infection may also occur. Rapidly growing mycobacteria include three clinically relevant species: *M. fortuitum, Mycobacterium chelonae,* and *M. abscessus*. Pulmonary disease due to rapidly growing mycobacteria is predominantly due to *M. abscessus*. It has a progressive and slow course that can cause death if left untreated.

## DIAGNOSIS

As recommended in the ATS statement, the diagnosis of pulmonary NTM disease should be based on an integrated assessment of clinical manifestations, radiographic findings, and laboratory data. These organisms are commonly found in nature, and contamination of culture material or transient infection does occur. Thus a single positive culture from sputum is insufficient for diagnosis but sufficient if the organism is isolated from a transbronchial or lung biopsy specimen as well as from a bronchial wash with high bacterial contents by either or both a smear and culture. To meet the current requirements for the diagnosis, examination of three separate sputum specimens should produce at least two positive cultures, with the third being at least smear-positive, or three positive cultures even from smear-negative specimens.[55]

Radiographically, NTM tend to cause thin-walled cavities with less surrounding parenchymal infiltrate; they are associated with less bronchogenic but more contiguous spread of disease; and they produce more marked involvement of pleura over the involved areas of the lungs. Occasionally, they may produce dense pneumonic disease or a solitary pulmonary nodule without cavitation. In the case of rapidly growing mycobacteria, radiology usually shows multilobar or predominantly upper-lobe infiltrates. They can be of patchy, reticulonodular, or mixed interstitial-alveolar type. Cavitation takes place in about 15 percent of patients.[56]

## MEDICAL TREATMENT

Most first-line anti-TB drugs have 10 to 100 times less *in vitro* activity against *M. avium* complex isolates than against *M. tuberculosis*. This diminished activity may be due to the lipophilic cell wall of *M. avium* complex, which prevents drug penetration. Clarithromycin and azithromycin have been found to be the most effective drugs in therapy of infections caused by *M. avium* complex and some other NTM, either pulmonary or disseminated (e.g., in patients with AIDS).[56] The three-drug regimen of clarithromycin, ethambutol, and rifabutin appears to be the most promising in the therapy of the disseminated *M. avium* infection in AIDS patients.

The current recommendation for the treatment of pulmonary disease caused by *M. kansasii* in adults is the regimen of isoniazid, rifampin, and ethambutol given daily for 18 months with at least 12 months of negative sputum cultures. In patients who are unable to tolerate one of these three drugs, clarithromycin would seem a reasonable alternative. Pyrazinamide is unacceptable as an alternate or third drug for *M. kansasii* because all isolates are resistant.[55] The treatment of lung disease due to the rapidly growing mycobacteria is generally difficult because of their resistance to virtually all antimycobacterial drugs.[56] *M. fortuitum* is usually susceptible to other oral antimicrobial agents including the newer macrolides (clarithromycin and azithromycin) and quinolones, doxycycline and minocycline, and sulfonamides. Combination therapy of low-dose amikacin plus high-dose cefoxitin for 2 to 4 weeks almost invariably produces clinical and microbiologic improvement in *M. abscessus* infection. Imipenem appears to be a reasonable alternative to cefoxitin.

## SURGICAL TREATMENT

For patients with MAC, if there has been poor response to drug therapy or if the patient's isolate has become macrolide-resistant, resectional surgery should be considered, especially if the disease is localized. Recent series even in the era of macrolide therapy have shown high sputum-negative conversion rates after surgery, although with relatively high morbidity.[57] There is a high incidence of bronchopleural fistula even with the use of a pedicle flap closure, especially after right pneumonectomy in patients with MAC. Whenever possible, this surgery should be performed at centers with thoracic surgeons who have considerable experience with this type of surgery. Overall, the bilateral nature of MAC lung disease, the advanced age of the patients, and the frequency of underlying chronic lung disease have limited the number of patients who are good candidates for surgery. With the advent of rifampin-containing regimens, surgery is now considered to have no role in managing routine cases of pulmonary disease due to *M. kansasii*.

For the rapidly growing mycobacteria, surgery is generally indicated with extensive disease, abscess formation, or in instances where drug therapy is difficult. Surgical resection for limited disease related to prior localized lung disease can also be curative especially in infections due to *M. abscessus.*

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## THORACIC INFECTIONS BOARD REVIEW QUESTIONS (CHAPTER 6)

1. Which of the following is not an indication for surgical resection of lung abscess?
   A. Cavity size >4 cm
   B. Suspected cavitating neoplasm
   C. Infected pulmonary sequestration
   D. Bronchopleural fistula
   E. Recurrent hemoptysis

2. Which is the most common indication for surgical intervention in pulmonary actinomycosis?
   A. Abscess
   B. Bronchopleural fistula
   C. Empyema
   D. Suspected carcinoma
   E. Hemoptysis

3. Which is true regarding nocardiosis?
   A. It is not associated with immunosuppression
   B. Characterized by sulfur granules draining from a chest wall sinus
   C. Responds to high-dose penicillin
   D. Commonly requires lobectomy
   E. Typically forms a solitary encapsulated abscess

4. Which is not an indication for surgical intervention in tuberculosis?
   A. Diagnosis of mediastinal lymphadenopathy
   B. Persistent cavitary disease with subsequent aspergillus colonization
   C. Continued sputum positivity with DR-Tb
   D. Bronchial stenosis
   E. Miliary tuberculosis

5. Which is not an indication for surgery in histoplasmosis?
   A. Middle lobe syndrome
   B. Healed solitary pulmonary nodule after adequate medical therapy
   C. Symptomatic broncholithiasis
   D. Superior vena cava obstruction
   E. Esophageal obstruction

## ANSWERS

1. **Answer: A.** Cavity size should be larger than 6 cm in order to proceed with operation. Suspected cavitating neoplasm, infected pulmonary sequestration, bronchopleural fistula, and recurrent hemoptysis are all indications for surgical intervention.
2. **Answer: D.** Suspicion of underlying carcinoma is the most common indication for surgery in pulmonary actinomycosis.
3. **Answer: B.** Nocardiosis is characterized by sulfur granules on microscopy recovered from the draining chest wall sinus. It is often associated with immunosuppression and responds to the combination of trimethoprim and sulfdamethoxazole. Because it usually presents as widespread infection, pulmonary resection is rarely indicated.
4. **Answer: E.** Widespread disease is not amenable to surgical resection. Complications of tuberculosis infection, including persistent cavitation and bronchial stenosis, should undergo surgical repair after adequate antimicrobial therapy.
5. **Answer: B.** If adequate medical therapy is completed, there is no indication for resection of a solitary pulmonary nodule consistent with histoplasmosis. Complications of histoplasmosis include fibrosing mediastinitis, which can result in middle lobe syndrome, SVC obstruction, and esophageal obstruction. Surgical repair is indicated for these patients as well as those developing symptomatic broncholithiasis from calcified nodes.

7

# Surgical Management of Emphysema

*Alex G. Little*

**KEY CONCEPTS**

- Epidemiology
  - It is estimated that two to three million patients suffer from emphysema.
- Pathophysiology
  - Except for rare cases caused by enzyme deficiency, smoking is the cause of diffuse emphysema. The smoke destroys lung tissue in an irreversible fashion leading to bullous formation. The bullae may be relatively small or quite large.
- Clinical features
  - Patients are hypoxic and dyspneic. The dyspnea ranges from mild to the need for home oxygen supplementation with subsequent diminishment in the quality of life.
- Diagnostics
  - Clinically, emphysema is a subset of chronic obstructive pulmonary disease (COPD). The other causes of COPD including chronic bronchitis and hyperreactive airways can coexist. Emphysema is diagnosed by pulmonary function testing that shows a decrease in forced expiratory volume in 1 second ($FEV_1$) and increase in total lung capacity and residual volume.
- Treatment
  - Medical: Cessation of smoking eliminates progression of the disease but the tissue loss is irreversible.
  - Surgical: Appropriately selected patients benefit from lung volume reduction surgery and/or resection of giant bullae. Operative mortality is minimal. Operative morbidity is significant but most patients recover and benefit with an improved quality of life.

## INTRODUCTION

### Pathophysiology

Emphysema is a pulmonary disease that is one of the conditions that are together characterized as chronic obstructive pulmonary disease (COPD). The other diseases that are also constituents of the diagnosis of COPD are chronic bronchitis, formally defined as the presence of a productive cough for any three months of any two consecutive years, and hyperreactive airway conditions, particularly asthma. Any of these three disease processes can exist independently, but some overlap and coexistence is common. Figure 7-1 displays and discusses the interrelationships between these subsets of COPD which typically coexist.[1] "Asthma" in the figure should be understood as representing all hyperreactive airway conditions. The important understanding is that pure emphysema is uncommon.

Emphysema literally means to inflate. As illustrated in Fig. 7-2, emphysema is defined as enlargement of the airways distal to the terminal bronchiole in association with destruction of the normal architecture.[2] This is a result of a permanent and irreversible loss of alveolar septi as well as loss of the elastic tissues. This tissue loss is not recoverable and distinguishes emphysema from compensatory air space distention that, for example, is frequently seen in the remaining lung following pneumonectomy. Nearly all emphysema is secondary to the injury caused by cigarette smoke although there is a rare hereditary abnormality that is associated with $\alpha_1$-protease inhibitor deficiency.

After the cigarette smoke has damaged the airways and parenchyma causing loss of tissue and destruction of anatomic integrity, the natural tendency is for continued enlargement of the air spaces distal to the terminal bronchial. Although this disease progression is caused by multiple factors, the predominant factor is now thought to be continued

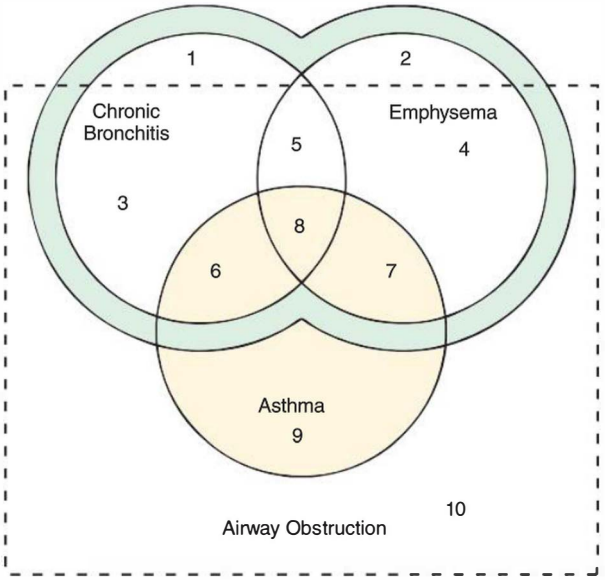



**FIGURE 7-1** Schema depicting chronic obstructive pulmonary disease (COPD). A nonproportional Venn diagram shows subsets of patients with chronic bronchitis, emphysema, and asthma in three overlapping circles. Subsets of patients lying within the rectangle have airway obstruction. Patients with asthma (subset 9) are defined as having completely reversible airway obstruction and lie entirely within the rectangle; their diagnosis is unequivocal. Patients in subsets 6 and 7 have partially reversible airway obstruction with chronic productive cough or emphysema, respectively. Patients in subset 8 have features of all three disorders. It may be difficult to ascertain whether patients in subsets 6 and 8 indeed have asthma or whether they have developed bronchial hyperreactivity as a complication of chronic bronchitis or emphysema; the history helps. Patients in subset 3 have chronic productive cough with airway obstruction but no emphysema; it is not known how large this subset is, because epidemiologic studies with the CT scan, the most sensitive in vivo imaging technique for the diagnosis or exclusion of emphysema, are not available. It is much easier to identify patients with emphysema determined by chest radiograph who do not have bronchitis (subset 4). Most patients who require medical care for their disease fall into subsets 5 and 8. Patients in subsets 1 and 2 do not have airway obstruction as determined by the $FEV_1$ but have clinical or radiographic features of chronic bronchitis or emphysema, respectively. Because COPD, when defined as a process, does not have airway obstruction as a defining characteristic, and because pure asthma is not included in the term COPD, patient subsets 1 to 8 are included within the areas outlined by the shaded band, which denotes COPD. (Reproduced with permission from Snider GL, Faling LJ, Rennard SI. Chronic bronchitis and emphysema. In: Murray JF (ed). *Respiratory Medicine*, 2nd ed. Philadelphia: WB Saunders, 1994:1334. Copyright Elsevier.)

traction on the damaged and weakened areas by the unopposed traction by the elastic tissue of the surrounding and less-damaged lung. These air spaces enlarge and eventually coalesce and are defined as bullae when their diameter is 2 cm or more. The expression "bullous" does not identify any particular size and the actual size may be as small as 2 cm or considerably larger, constituting the so-called giant bullae. All emphysema is bullous but the sizes of the bullae

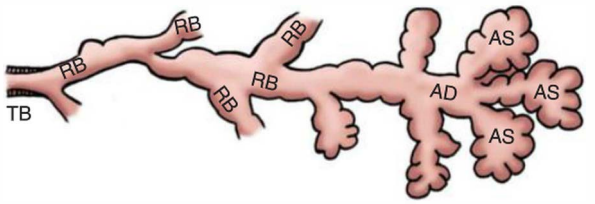



**FIGURE 7-2** This drawing shows normal respiratory airway anatomy. Emphysema affects the functional units, which are those distal to the terminal bronchiole (TB), the last airway to have cartilage in its wall. RB, respiratory bronchiole; AD, alveolar duct; AS, alveolar sac. (Reproduced with permission from Little AG. Surgical treatment of emphysema. In: Cameron JL, Balch CM, Langer B, et al. (eds). *Advances in Surgery*, Mosby, 1997:191. Copyright Elsevier.)

vary considerably. In most patients, the disease and the bullae are diffuse throughout the lung, although upper-lobe disease is more common than the lower-lobe disease. As the disease progresses and the bullae distend further, the actual lung size as well as total and residual lung volumes increase. Ultimately, the increase in lung volume and size causes an anatomic change in the chest with an increase in chest size including the anteroposterior dimensions of the rib cage with downward flattening of the diaphragm.

The most important physiologic alteration with diffuse emphysema is an increased tendency to premature collapse of smaller airways during expiration. The primary factor for this is the loss of normal elastic tissue with the recoil properties that hold the bronchioles open, although there is some compression of functional tissue by the bullae or air spaces. As pleural pressure increases during expiration, the relatively unsupported airways close, trapping air that is measured as residual volume.

Large or so-called giant bullae are relatively uncommon. They are usually multiple and nearly always associated with true, diffuse emphysema in the rest of the lung. The pathophysiology of these giant bullae is a variation on the previously described theme of diffuse, bullous emphysema. Once an area of parenchymal weakness is of sufficient size, it continues to fill with air preferentially. The force of elastic recoil in the better lung then retracts away from the bulla. The surrounding lung is not, as previously thought, compressed by high pressure within the bulla. Rather, the relatively more normal lung retracts away from the bulla and the lack of elastic recoil in adjoining airways leads to occlusion and atelectasis.

## Clinical Features

Although many patients with emphysema will also have bronchitis and/or hyperreactive airways, the following symptoms are typical. Dyspnea or difficulty breathing is the most frequently encountered symptom and generally present in all patients. Depending on the severity of the disease, this may occur at rest, even requiring oxygen supplementation, or may be more subtle and manifested by a decrease in exercise

tolerance. Many patients also have a cough that may or may not be productive of sputum. Wheezing is another very common symptom as well as excess mucous production. Some patients may exhibit cyanosis. In all circumstances, emphysema results in a diminished ability to deliver oxygen to the tissues. For example, if the brain is not receiving enough oxygen, the patient may demonstrate irritability, confusion, and/or mental instability.

# DIFFUSE EMPHYSEMA

## Diagnosis

The hallmark of emphysema is air-flow obstruction during expiration caused by the collapse of small airways that have lost the usual surrounding elastic tissue which promotes airway expansion. Pulmonary function testing (PFT) is essential to establish the diagnosis. Spirometry indicates expiratory air-flow obstruction with a reduction in the forced expiratory volume in 1 s ($FEV_1$) as well as a reduction in the ratio $FEV_1$/FVC (forced expiratory capacity). With worsening severity of the disease, lung volumes increase which leads to increases in total lung capacity, functional residual capacity, and residual volume. Further, eventually the diffusing capacity to carbon monoxide (DLCO) diminishes, which is a result and a measure of the severity of the parenchymal destruction and tissue loss characteristic of emphysema.

## Medical Therapy

Smoking cessation is essential and by far the most important therapeutic maneuver available to treat patients. Although not curative, middle-aged smokers who stop smoking experience a significant improvement in the rate of decline in pulmonary function and return to the annual changes seen in nonsmokers. To achieve this benefit, all possible aid to achieve this goal should be provided to these patients, including the use of pharmacologic agents and nicotine-replacement therapy.

Bronchodilator agents (both oral and inhalers) can also provide symptomatic benefit in patients with COPD and, in particular, those with emphysema. The inhaled route is preferable as side effects are less common with this route compared with parenterally delivered medications. β-Agonist drugs, such as albuterol, which are also bronchodilators, provide symptomatic benefit. Side effects including tremor and tachycardia are associated with these agonists.

The use of glucocorticoids is mildly controversial. Although inhaled glucocorticoids can reduce the frequency of disease exacerbations, their use has been associated with increased rates of oral pharyngeal candidiasis and bone density loss. In general, the chronic use of oral glucocorticoids is not recommended because of what is considered to be an unfavorable risk-to-benefit ratio.

## Surgical Therapy

### INDICATIONS

The history of surgery for emphysema is a fascinating one.[2,3] On the basis of flawed but well-intentioned logic, the early 20th century first saw interest in surgical enlargement of the chest cavity and therefore presumably lung capacity by operations such as transverse sternotomy with costochondrectomy. Initially employed in horses, this operation failed to improve pulmonary function. Subsequently, on the basis of the observation that the chest and lungs in emphysema patients were abnormally large, operations to reduce chest capacity became attractive. Accordingly, procedures such as reduction thoracoplasty and even phrenic nerve interruption to elevate the diaphragm were performed. Again, benefits did not result from these approaches.

Surgical efforts culminated in the 1950s and 1960s with a series of reports from Brantigan.[4–6] His prescient insight into the pathophysiology of emphysema led him to conclude that removal or exclusion of volume occupying, peripheral, and bullous regions of the lung would improve pulmonary function by restoring the chest wall to a more effective configuration. He also reasoned that, with resection of the diseased lung, the more normal remaining lung would be expanded by its preserved elastic recoil properties. Applying his theories to patients, the operations he performed were successful in improving pulmonary function in operative survivors, but the operations were associated with unacceptably high perioperative mortality rates and ultimately failed, in part because patients continued to smoke postoperatively. Consequently, this approach to emphysema patients was abandoned.

Brantigan's ideas and concepts were resuscitated in the 1990s. The first report by Wakabayashi and colleagues used a video-assisted thoracic surgical (VATS) approach and laser contraction/consolidation of the peripherally diseased areas.[7] Ultimately, this approach was shown to be less effective than operative resection of the more diseased areas when this concept was reintroduced by Cooper and his associates in 1994.[8]

The current operative procedure is termed lung volume reduction surgery (LVRS). Due to controversies and uncertainties surrounding patient selection for LVRS and, to a lesser extent, operative technique (i.e., sternotomy or VATS), a multi-institutional prospective, randomized investigation, identified as the National Emphysema Treatment Trial (NETT), was conducted. The impact of multiple clinical and laboratory variables on perioperative and long-term outcomes was assessed as LVRS was compared with "maximal" medical management in a prospective and randomized fashion. Tables 7-1 and 7-2 provide a detailed summary of the NETT conclusions regarding the indications and appropriate patient selection for LVRS.[9,10] In general, patients who benefit the most from LVRS are those with a low exercise capacity and upper-lobe predominant, heterogeneously distributed emphysema. Figure 7-3 is an illustrative chest CT scan. The upper lobes display severe emphysematous change,

**TABLE 7-1: Common Inclusion and Exclusion Criteria for Lung Volume Reduction Surgery**

| |
|---|
| **Inclusion criteria** |
| Radiographic evidence of emphysema, especially involving upper lobes |
| Hyperinflation |
| $FEV_1$ >20 and <45% predicted (postbronchodilator) |
| DLCO >20% predicted |
| Severe dyspnea |
| Restricted activities of daily living |
| Decreased quality of life |
| Abstinence from tobacco |
| **Exclusion criteria** |
| Active smoking |
| Bronchiectasis |
| Pulmonary nodule requiring evaluation |
| Excessive daily sputum production |
| Previous thoracotomy |
| Obvious pleural disease |
| Active or inducible coronary ischemia |
| Pulmonary hypertension |
| Depressed LVEF (<45%) |
| Obesity |
| Systemic steroids ≥20 mg prednisone/day |

DLCO, diffusion capacity for carbon monoxide; LVEF, left ventricular ejection fraction.

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whereas the lower lobes are much less diseased. Appropriate candidates experience dyspnea that restricts their activities related to daily living and diminishes their quality of life. These characteristics must be present despite the patient's compliance with an appropriate medical regimen, including smoking cessation. On the other hand, the patient must have sufficiently diminished pulmonary function to require intervention but enough reserve to both tolerate the operation and possess the capacity for improvement. Appropriate LVRS candidates can, in part, be identified as having an $FEV_1$ greater than 20 percent of predicted but less than 45 percent. Tables 7-1 and 7-2 provide additional criteria used to identify appropriate and reasonable candidates for LVRS.

## LVRS Techniques

As for surgical technique, no difference in outcomes in terms of subjective or objective measures of pulmonary function between open and minimally invasive approaches was identified by NETT. However, the VATS approach resulted in earlier recovery at a lower cost compared with sternotomy.[11,12] Analogous to reports of patients undergoing VATS lung cancer resection documenting less pain, shorter hospital stays, and earlier chest tube removal compared with patients undergoing thoracotomy.[13] For these reasons, the VATS approach is most frequently employed for LVRS at present.

Independent of the approach, the operative goal for LVRS is to resect the most diseased lung parenchyma. These regions are, as mentioned, almost exclusively located in the upper lobes. The location of these regions is suggested by preoperative lung ventilation/perfusion and chest tomographic scans, and is definitively identified intraoperatively as the lung areas that are slowest to deflate when single-lung ventilation of the contralateral lung is instituted. Gentle handling of these fragile tissues and careful lysis of adhesions to the chest wall as the lung is mobilized are critically important to minimize lung trauma and the incidence and severity of postoperative air leaks. A linear stapler with buttressing material is used to resect the diseased areas. The buttressing adds integrity to the staple line, thereby minimizing postoperative air leaks. As the disease is diffuse, both lungs are involved. A sternotomy is therefore used for bilateral access when an open approach is used. The appropriate resection is performed on one lung during single-lung ventilation of the contralateral lung. This sequence is then reversed. For the VATS approval, the patient can be turned from one side to the other, allowing sequential left and right lung resections. Alternatively, the patient can be positioned so that both pleural spaces can be accessed without the need for repositioning.

## LVRS Outcomes

The postoperative management of patients after LVRS is frequently challenging. NETT identified that patients with an $FEV_1$ of 20 percent or less of predicted and either a DLCO of 20 percent or less of predicted or a homogeneous pattern of emphysema on chest CT was associated with a high perioperative risk of death and should not be considered appropriate candidates for LVRS.[14–16] Among patients without these high-risk factors, the 30-day mortality rate after LVRS was 2.2 percent compared with 0.2 percent in the medical therapy group. However, mortality rates among patients who are not at high risk were comparable. Mortality was 0.09 deaths per person-year in the surgery group compared with 0.10 deaths per person-year in the medical therapy group (risk ratio, 0.89; $p = 0.31$). When patients are appropriately selected, LVRS does not affect overall mortality. However, LVRS does expose patients to perioperative morbidity. Morbidity is minimized by selection of appropriate surgical candidates and having patients in maximal physiologic condition where pulmonary function has been optimized with a preoperative 6 to 10 weeks pulmonary rehabilitation program. Attention to nutritional needs, as approximately half of all emphysema patients are deficient nutritionally, is also helpful.[17] Despite these maneuvers, 58.7 percent of patients in the NETT trial experienced at least one complication.[18] Cardiac dysrhythmias, the most common complication,

**TABLE 7-2: Criteria for Determination of Candidacy for Lung Volume Reduction Surgery**

| Criteria | Good Candidates | Poor Candidates |
|---|---|---|
| History and physical examination | Age <75 years | Age ≥75 years |
| | Emphysema by clinical evaluation | History of recurrent bronchial infections with increased sputum production |
| | Ex-smoker >4 months | Cardiovascular comorbidities including significant coronary artery disease, recent MI, CHF, or uncontrolled hypertension or arrhythmias |
| | Clinically stable on no more than 20 mg prednisone daily | Pulmonary hypertension at rest |
| | Significant functional limitation after 6–12 weeks of pulmonary rehabilitation on optimal medical therapy | Nonpulmonary comorbidities causing significant functional limitation (morbid obesity) or that could limit survival (e.g., cancer) |
| | Demonstrated compliance with medical regimen | History of thoracic surgery or chest wall deformity that could interfere with pulmonary resection |
| Laboratory evaluation | Postbronchodilator $FEV_1$ ≤45% predicted for all ages and ≥15% if age ≥70 years | $FEV_1$ ≤20% predicted and either DLCO ≤20% predicted or homogeneous distribution of emphysema on HRCT scan |
| | Hyperinflation demonstrated by TLC ≥100% predicted and RV ≥150% predicted | Non-upper-lobe distribution of emphysema with high exercise capacity postrehabilitation (demonstrated by maximal achieved cycle ergometry watts) |
| | Postrehabilitation 6MWD >140 m | Significant pleural or interstitial changes on HRCT |
| | Low postrehabilitation exercise capacity (demonstrated by maximal achieved cycle ergometry watts) | |
| | HRCT demonstrating bilateral severe emphysema, ideally with upper lobe predominance | |

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occurred in 23.5 percent of patients, with treatment required in 18.6 percent. Pneumonia was identified in 18.2 percent of patients. Predictably, pulmonary insufficiency was an issue and 21.8 percent of patients required at least one reintubation, tracheostomy was necessary in 8.2, and 5.1 percent could not be weaned from mechanical ventilation within 3 days of LVRS.

Prolonged air leaks following LVRS are a frustrating persistent issue contributing to postoperative morbidity.[10,19,20] In the NETT experience, 90 percent of patients experienced an air leak in the first 30 days after LVRS. Overall, the median duration of the air leak was 7 days and 66 of 496 (13.3%) patients suffered from air leaks that persisted 30 days or longer following their operation. Neither the surgical approach (i.e., open vs. VATS), choice of suture line buttressing material, performance of pleurodesis, nor construction of pleural tents was shown to affect either the incidence or the duration of the air leaks. Postoperative chest tube management with use of no or low (e.g., 10 mm Hg) negative pressure suction may be helpful by lessening the air flow through the visceral pleural defects.[19,20] Finally, patients with persistent air leak can be discharged from the hospital with a Heimlich valve placed on the chest tube to be removed when the air leak ceases.

Although LVRS does not provide a survival advantage, the benefit for LVRS patients is in their improved quality of life. The NETT study revealed that changes in exercise capacity, the 6-min-walk distance, percentage improvement in $FEV_1$, quality of life, and the degree of dyspnea at 6, 12, and 24 months favored patients undergoing LVRS[14,15] over those receiving maximal medical management. Although the number of patients who ultimately qualify for and undergo LVRS may not be large, the positive impact on appropriate patients is significant.

Another important benefit seen with LVRS is the reduction of health care costs.[12] In the first 12 months after randomization to treatment in the NETT trial, the total cost per patient was higher in the LVRS group than the medical group due to the cost of the operation and postoperative hospitalization. However, after 3 years, the cost-effectiveness ratio for LVRS compared with medical treatment was US$190,000 per quality-adjusted life-year gained per patient.

## Bronchoscopic Techniques

As LVRS is associated with significant mortality, morbidity, and costs, three bronchoscopic lung volume reduction (BLVR) approaches are currently being evaluated as potential alternatives to LVRS. The goal is to achieve a remodeling of the lung with exclusion and subsequent collapse of the same diseased lung areas resected during LVRS. The three

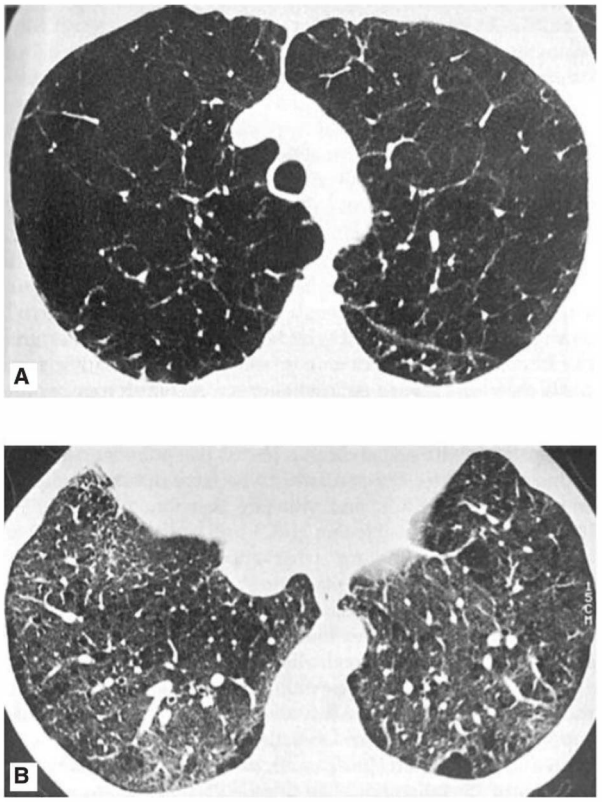



**FIGURE 7-3** Severe centrilobular emphysema in a patient being assessed for lung volume reduction surgery. The distribution of emphysema is markedly heterogeneous. **A.** Emphysema is concentrated mainly in the upper lobes. **B.** By comparison, the lower lobes are relatively spared. (Reproduced with permission from Hansell DM, Armstrong P, Lynch DA, McAdams HP. *Imaging of Diseases of the Chest*, 4th ed. Philadelphia: Elsevier Mosby, 2005:761. Copyright Elsevier.)

approaches currently being investigated include (1) placement of one-way valves in the appropriate bronchus to allow distal atelectasis and collapse of the targeted lung region by blocking inspiratory air flow, (2) use of a radiofrequency catheter to create a shunt pathway between a central airway and a region of hyperinflated lung to facilitate emptying of diseased lung regions that have delayed expiratory times, and (3) instillation of biological adhesives as separate liquid components that polymerize distally at the target sites, leading to alveolar collapse and ultimately remodeling of the hyperinflated areas.

## Bronchoscopic Outcomes

BLVR is performed to exclude the hyperinflated lung areas and achieve an anatomic and physiologic situation that resembles the outcomes of LVRS without the need for an operative procedure with its attendant morbidity and mortality. Up until now, results have been inconsistent and are not yet on a par with LVRS.[21,22] Consequently, BLVR is still considered to be an investigative procedure to be evaluated further. Most patients do not have the same objective improvements in exercise capacity and pulmonary function variables seen following LVRS, suggesting that much of the subjective improvement seen in BLVR patients may be related to a placebo effect.

## Lung Transplantation

Emphysema is currently the most common indication for lung transplantation, accounting for nearly half of all lung transplants.[23] The criteria for patient selection are essentially the same as those for LVRS. Although the original interest in lung transplantation was motivated by interest in prolonging life, a survival benefit has not been demonstrated. Actual benefits do occur but are related to documented improvements in quality of life through improvement in pulmonary function and exercise capacity. Ongoing uncertainties relate to the choice between LVRS and lung transplantation as the better alternative and whether single- or double-lung transplantation is the most appropriate procedure. The early hope that LVRS could serve as a bridge to transplantation has been diminished by the observation that prior LVRS increases the risk of bleeding during transplantation and is considered by some as a relative contraindication to transplantation for this reason.[23] Furthermore, the limited availability of donor lungs for transplantation limits its broad application to this patient population.

# GIANT BULLOUS EMPHYSEMA

## Diagnosis

Clinical and PFT characteristics of emphysema have been discussed and they all apply to patients with giant bullous disease. These patients cannot be differentiated from diffuse emphysema patients by their symptoms or other clinical criteria. The distinctive feature and distinguishing findings in these patients are large bullae as seen on either chest x-ray or chest CT scan. These bullae occupy a significant portion of the chest cavity and the remaining lung is significantly compressed. Figure 7-4 illustrates the typical chest CT scan appearance of bilateral large bullae with compression of the adjacent relatively normal lung.

## Medical Therapy

As these patients have diffuse emphysema along with large bullae, they can be helped through the medical interventions previously described, particularly through cessation of smoking. This initial approach may be sufficient to eliminate the need for surgical intervention. At present, however, there is no procedural modality that is specifically effective for giant bullous emphysema.

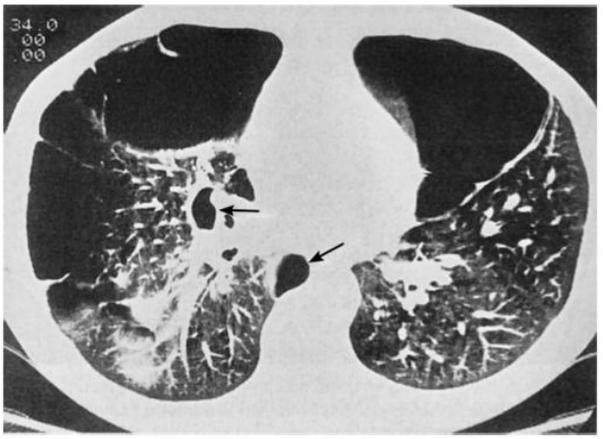


**FIGURE 7-4** Bullous disease on CT. Several large bullae are situated anterolaterally. Smaller bullae (arrows) are present in the azygoesophageal recess and against major vessels. Intervening lung, well seen paravertebrally, is reduced in volume but is otherwise normal and contains well-preserved vessels. (Reproduced with permission from Hansell DM, Armstrong P, Lynch DA, McAdams HP. *Imaging of Disease of the Chest*, 4th ed. Philadelphia: Elsevier Mosby, 2005:764. Copyright Elsevier.)

## Surgical Therapy

### INDICATIONS

Potential beneficiaries of surgical resection of giant bullous disease, namely bullectomy, are patients with both significant dyspnea that limits daily activities and nonfunctioning bullae that are large enough to compress the adjacent normal lung parenchyma. A chest CT scan with intravenous contrast helps identify those patients who will benefit from surgery. If a bulla or several bullae are shown to occupy a third or more of the hemithorax, bullectomy is likely to improve oxygenation translating into improved pulmonary function and an improved quality of life for the patient. Furthermore, reduced blood flow to the adjacent and compressed lung parenchyma, demonstrated on CT or pulmonary arteriogram, also suggests benefit from bullectomy.

### TECHNIQUES

Operations for diffuse emphysema include VATS or an open technique via thoracotomy for unilateral bullae or sternotomy for bilateral large bullae.[24–26] Regardless of the approach, the operation begins with single-lung ventilation of the contralateral lung. As the lung to be resected slowly deflates, the bullous extent is clearly identifiable. The roof of the bulla is incised, thus opening it and exposing its interior. Most of the bullous wall is excised, leaving a rim of 2 to 3 cm of residual wall. The base of the bullae is stapled by placing the stapler just on the adjacent true parenchyma, taking care not to remove potentially functional lung tissue. The remaining bullous wall is folded into the stapler where it serves as buttress material within the staple line, reducing the likelihood of severity and duration of postoperative air leaks.

### OUTCOMES

The reported perioperative mortality rate for bullectomy ranges from 2.3 percent to 10 percent, with most deaths related to pulmonary failure.[24–26] The perioperative course is similar to that of LVRS patients as postoperative complications occur in more than half of the patients. Cardiac dysrhythmias, pneumonia, and pulmonary insufficiency constitute the most common causes of morbidity, just as with LVRS. Preoperative optimization of the patient's pulmonary function with cessation of smoking, bronchodilator therapy, and participation in a rehabilitation program are again important and serve to reduce complications. The most common complication is a prolonged air leak defined as lasting more than 7 days. Drawing from the LVRS experience, applying minimal or no suction to the chest tube(s) may reduce the frequency with which this complication occurs.[19,20]

The long-term postbullectomy impact on quality of life and pulmonary function has not been as thoroughly assessed as in the NETT study. However, several reported experiences have identified both clinical and functional improvement for at least 5 years after bullectomy.[24–26] This improvement in quality of life correlates with improved $FEV_1$, decreased residual volumes, and improved vital capacity noted in appropriately selected patients.

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## SURGICAL MANAGEMENT OF EMPHYSEMA BOARD REVIEW QUESTIONS (CHAPTER 7)

1. The pathogenesis of emphysema is related to:
   A. Smoking related increase in mucous production
   B. Smoking related tissue destruction
   C. Effects of aging
   D. Primary diaphragmatic dysfunction
   E. Radon exposure

2. Tissue destruction from emphysema is typically most severe in the:
   A. Upper lobes
   B. Lower lobes
   C. Perihilar areas
   D. Diffusely throughout
   E. Right lung

3. The most suitable candidate for lung volume reduction surgery would have which of the following findings on pulmonary function testing? (Percents are percent of the predicted value.)
   A. $FEV_1$ between 30 and 60 percent; increased TLC
   B. $FEV_1$ between 30 and 50 percent; decreased TLC
   C. $FEV_1$ between 20 and 40 percent; increased TLC
   D. $FEV_1$ between 20 and 40 percent; decreased TLC
   E. Normal RV and normal TLC

4. The following operative measure(s) have been shown to reduce the duration and severity of air leak after LVRS.
   A. Formation of a pleural tent
   B. Use of biological sealant spray
   C. Buttressing of the staple line
   D. All of the above
   E. None of the above

5. Giant bullae:
   A. Occur in normal as well as emphysematous lungs
   B. Are an indication for surgery
   C. Cannot be resected with VATS
   D. Regress if the patient stops smoking
   E. Compress adjacent lung parenchyma

## ANSWERS

1. **Answer: B.** Smoke and its constituents damage lung parenchyma in an irreversible fashion. When sufficient damage has occurred, air spaces called bullae are formed and the result is bullous emphysema.
2. **Answer: A.** While emphysema is generally diffuse and present in both lungs, the upper lobes typically manifest the most severe disease.
3. **Answer: C.** All patients have an increased RV and TLC because of air trapping during expiration. The NETT showed that the most suitable candidate for LVRS will have an $FEV_1$ between 20 and 40 percent.
4. **Answer: E.** None of the maneuvers listed has been shown to be efficacious in reducing the duration or the severity of air leak.
5. **Answer: E.** Giant bullae are a result of emphysema. They can be resected thoracoscopically but only when corrective measures fail. They do not regress. They do compress the remaining lung.

# 8

# Tracheal Diseases

*Dan J. Raz*
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## KEY CONCEPTS

- Epidemiology
  - Primary tracheal tumors are rare, with an estimated 2.7 new cases diagnosed per million persons per year. The many remaining tracheal pathologies comprise heterogeneous epidemiologies.
- Pathophysiology
  - Congenital tracheal stenosis may present as a web-like diaphragm, most often at the subcricoid level. Primary tracheal tumors are largely (about two-thirds) made up of adenoid cystic and squamous cell carcinomas with roughly equal histologic frequency. Other tumors include pleomorphic adenomas, leiomyomas, chondromas, carcinoid tumors, mucoepidermoid tumors, and sarcomas. The laryngotracheal junction is the most frequent location of injury in airway trauma. Most tracheoesophageal fistulas are complications from mechanical ventilation.
- Clinical features
  - Patients with tracheal pathology usually present with signs and symptoms of upper airway obstruction: dyspnea on exertion, wheezing, stridor, and obstructive pneumonia. Tracheal tumors most commonly present with cough, hemoptysis, and signs of progressive airway obstruction, although signs and symptoms vary with tumor histology. Tracheoesophageal fistulas (TEFs) typically manifest as a sudden increase in tracheal secretions and ingested material in the trachea.
- Diagnostics
  - Anteroposterior and lateral tomography is useful to define upper tracheal pathology. Fluoroscopy demonstrates functional vocal cord asymmetry and other details (e.g., airway collapse with malacia). Computed tomography (CT) is helpful in malignant disease to assess extramural extent and lymphadenopathy. Inspiratory/expiratory CT is the easiest, most accurate noninvasive method to diagnose tracheomalacia. Flexible and rigid bronchoscopy is critical in the definitive assessment of the trachea.
- Treatment
  - Tracheal resection can be performed using a cervical or transthoracic approach, depending on the location and the extent of the lesion. Tracheal release maneuvers are primarily intended to prevent excessive tension on the anastomosis and avoid the need for excessive tracheal dissection.
  - Laryngotracheal injuries should be treated with airway establishment (e.g., tracheostomy). Traumatic lacerations of the lower trachea can be approached via partial or full sternotomy or right posterolateral thoracotomy.
  - Congenital tracheal stenoses may be treated with anterior tracheoplasty and patch repair or slide tracheoplasty.
  - Most TEFs require tracheal resection. Anastomotic complications are reduced if definitive single-stage correction of the fistula is delayed until after the patient has been successfully weaned from mechanical ventilation. Fistula control can be achieved by placing a tracheostomy with the balloon placed below the fistula, draining gastrostomy, and feeding jejunostomy.
  - Idiopathic laryngotracheal stenoses have been treated with complex, multistaged or single-stage procedures involving partial resection of the subglottic larynx and immediate plastic reconstruction.
- Outcomes/prognosis
  - At the Massachusetts General Hospital, operative mortality for primary tracheal tumor resection

has improved from 21 percent in the 1960s to 3 percent in the last decade. The overall 1-, 5-, and 10-year survival rates for primary tracheal carcinoma have been reported to be 84, 45, and 25 percent respectively. All tracheal surgery is subject to anastomotic complications, including suture line granulomas, stenosis, and tracheal separation. Predictors of anastomotic complications include reoperation, diabetes, lengthy resections, laryngotracheal resections, age 17 years or less, and preoperative tracheostomy. Anastomotic complications are associated with a 7.4-percent mortality, compared with 0.06 percent in patients who did not experience anastomotic complications.

# BACKGROUND

## Historical Perspective

Early in the evolution of tracheal surgery, it was believed that the amount of trachea that could be excised safely was four rings or approximately 2 cm. Because of this belief, much of the early work in this area focused on the use of prosthetics for tracheal replacement. Although early clinical reports of tracheal replacement with bioengineered materials have been reported,[1,2] consistent success is not yet attained for replacement of the airway.

In parallel with the efforts to find a suitable prosthetic device, efforts were underway to determine the possibilities of resection and primary reconstruction. Grillo and colleagues[3] systematically investigated the limits of resection of the trachea that might permit primary reconstruction without excessive tension and without destruction of its vital blood supply. Experiments in human cadavers demonstrated that the blood supply of the trachea entered in its lateral pedicles and that mobilization of the trachea is best accomplished only by anterior and posterior dissection. These studies concluded that a median length of 4.5 cm or approximately seven rings could be resected and primarily reconstructed with an acceptable amount of tension.

As the issues of extent of resection, methods of mobilization, limits of acceptable tension, and preservation of blood supply were established, primary resection and reconstruction became the accepted mode of managing most diseases that involved the trachea. Reports of resection and primary reconstruction of lengths of the trachea followed, which had been previously thought to be impossible.[4,5]

## Anatomy

The adult trachea measures 11 cm in average length from the anterior border of the cricoid cartilage to the carinal spur. There are 18 to 22 cartilaginous rings in the human trachea, with approximately two rings per centimeter. The only complete cartilaginous ring in the normal airway is the cricoid cartilage of the larynx. The remainder of the rings is C-shaped, connected posteriorly by the membranous portion of the trachea. The blood supply of the trachea is shared with the esophagus laterally and with the main bronchi below. Above, the blood supply originates from the inferior thyroid artery, and vessels to the lower trachea are derived from the bronchial vessels (Fig. 8-1). Importantly, branches of these vessels enter the trachea laterally.

# PATHOLOGY

## Congenital Lesions

Congenital tracheal stenosis may present as a web-like diaphragm, most often at subcricoid level. More lengthy stenoses may involve the entire trachea, sometimes with a

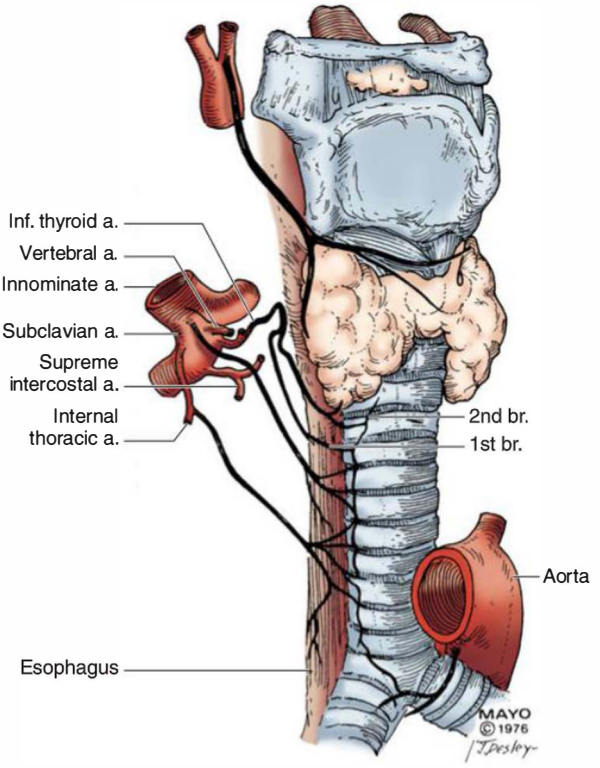



**FIGURE 8-1** Arterial supply to the thoracic trachea. Inf, inferior; a, artery; br, branch. [From Salassa JR, Pearson BW, Payne WS. Gross and microscopical blood supply to the trachea. Reprinted with permission from the Society of Thoracic Surgeons (*Ann Thorac Surg* 1977;24:100–107). By permission of Mayo Clinic.]

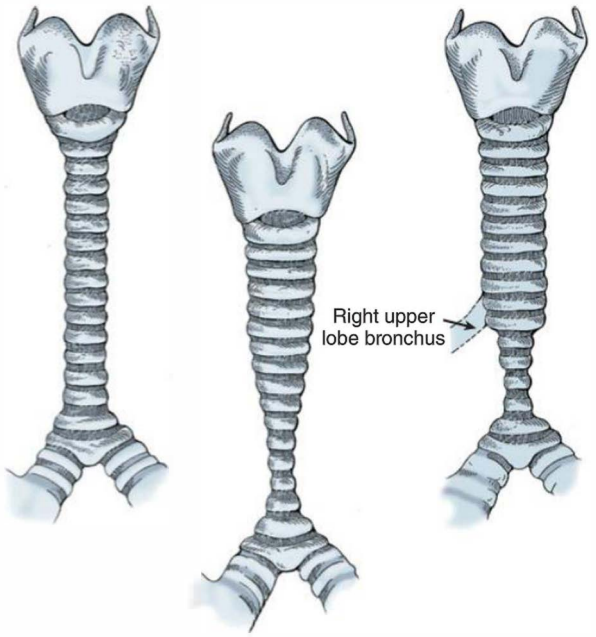



**FIGURE 8-2** Congenital tracheal stenosis. Type I (left): Generalized hypoplasia of the trachea. The airway has a normal caliber at the level of the cricoid cartilage and also in the main bronchi. Type II (center): Funnel-like narrowing. The trachea has a normal caliber immediately below the cricoid cartilage but funnels to its narrowest point, most frequently above the carina. Type III (right): Segmental stenosis may be accompanied by bronchial anomalies. The segmental stenosis may vary in length and may be at various levels. (From Cantrell JR, Guild HC. Congenital stenosis of the trachea. *Am J Surg* 1964;108:297. With permission. Copyright Elsevier.)

normal larynx and main bronchi, or they may involve variable lengths of the trachea (Fig. 8-2). Funnel-like narrowing is sometimes seen, with gradual narrowing to the stenotic segment. Segmental stenosis of the lower trachea may be accompanied by bronchial anomalies such as origin of all or part of the right upper-lobe bronchus from the trachea just above the stenotic segment. Most often the cartilaginous rings are circular in the area of stenosis. Other developmental anomalies may occur in a patient with congenital tracheal stenosis.

## Trauma

### EXTERNAL TRAUMA

The trachea, carina, and main bronchi may be damaged by either blunt or penetrating trauma. Blunt cervical injury may result in injury to the airway at any level from the hyoid bone to the carina.[6] Subcutaneous emphysema may be detected in the neck or, if the injury involves the more distal trachea, pneumomediastinum may be seen. Pneumothorax may result from tracheal injury within the chest cavity. Patients may present with varying severities of dyspnea from airway obstruction caused by these injuries or from tracheal transection. A patient with an initially satisfactory airway may rapidly decompensate while under observation or as intubation or examination of the airway is attempted.

If the airway is partially separated, a flexible bronchoscope with an endotracheal tube threaded over it is the best way to assess it. If difficulty is encountered, emergency tracheostomy should be quickly performed before the airway is lost. A completely transected trachea may retract into the mediastinum but is easily located by finger palpation and grasped by clamps and delivered into the field.

Blunt intrathoracic tracheal injury is a result of high-impact trauma, and as a result, it is usually associated with concomitant chest wall, pulmonary, and great vessel injury. Injuries to the carina and the main and lobar bronchi may occur from crush injuries to the chest. These tend to occur more frequently than tracheal injuries.

### INHALATIONAL INJURIES

Tracheal injury may also occur in the form of thermal or chemical damage by inhalation. Inhalation burns of the larynx, trachea, and bronchi may be particularly difficult injuries. The degree of inflammatory change, granulation tissue response, and scarring will depend on the depth of mucosal injury. In most cases, the tracheal rings are not destroyed. Resection is generally precluded, as lengthy injuries often occur. A number of cases of airway obstruction caused by burns have been managed initially by a tracheostomy placed at the second or third ring, typically within the area of burn injury, followed later by placement of a silicone T tube to span the injured area.

## Iatrogenic Injuries

### ACUTE INTUBATION INJURIES

Lacerations of the trachea during intubation occur most often in the membranous wall. These may be long and may also damage the esophagus, resulting in a tracheoesophageal fistula (TEF). Respiratory symptoms and concomitant esophageal injuries are indications for immediate repair.

### POSTINTUBATION INJURIES

Postintubation injuries to the trachea include granulomas, strictures, malacia, and tracheoesophageal and tracheoinnominate artery fistulas (Fig. 8-3).

Tracheal strictures represent the most common postintubation injuries. These occur principally at either the level of the tracheal stoma or that of the tracheal cuff. Both result from proliferative and cicatricial responses to tracheal injury. Granulomas result from erosion by the tip of a tracheostomy or endotracheal tube and can also occur at the site of a healed tracheostomy. Stomal stenosis results from

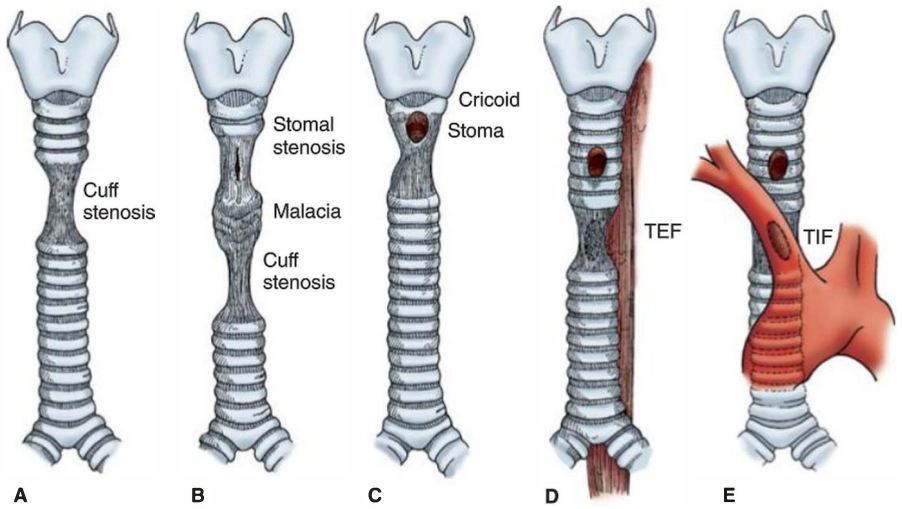



**FIGURE 8-3** Diagrams of principal postintubation tracheal lesions. **A.** Cuff stenosis from the cuff of an endotracheal tube. **B.** Cuff stenosis from the cuff of a tracheostomy tube, usually lower in the trachea than that from an endotracheal tube. Stomal stenosis also occurs at the site of the tracheostomy itself. Malacia may occur either at the level of the cuff or in the segment between the stoma and the cuff stenosis. **C.** Cuff stenosis at the site of a high tracheostomy stoma, which has eroded into the lower margin of the cricoid cartilage. In older patients, this may erode back further into the subglottic larynx, producing a laryngotracheal stenosis. **D.** Tracheoesophageal fistula (TEF) produced by pressure of the cuff against the membranous wall, often abetted by an indwelling firm nasogastric tube. **E.** One type of tracheoinnominate fistula (TIF), the result of a high-pressure cuff erosion. The more common type, but also rare, is that seen with a low-placed tracheostomy stoma, which rests against the innominate artery itself. Not shown here are the lesions that occur in the larynx as a result of endotracheal tubes. (From Grillo HC. Surgical management of postintubation tracheal injuries. *J Thorac Cardiovasc Surg* 1979;78:860. With permission. Copyright Elsevier.)

the gradual enlargement of a tracheal stoma and its eventual healing by contraction. This pulls the sides of the defect together, distorting the tracheal lumen to a triangular configuration with the base of the triangle located posteriorly, consisting of the uninjured membranous wall. The instigating large stoma may result from overzealous excision of tracheal wall at the time of the initial tracheostomy, from erosive infection around the margins of the stoma, or most commonly from erosion secondary to leverage by equipment attached to the tracheostomy tube during ventilation. The stenotic process may extend into the subglottic larynx if the previous tracheostomy was placed inappropriately high in the trachea.

Cuff stenosis, on the other hand, is caused by circumferential erosion of the trachea by excessive pressure exerted by the sealing cuff. In the healing process, cicatricial connective tissue is formed, which contracts in a circumferential fashion. The route of entry of the ventilatory tube does not affect the occurrence of cuff injury, only its level. These lesions are seen in patients who have had only endotracheal intubation as well as those with previous tracheostomy. Cuff injuries have been observed in patients with only 48 h of exposure to a high-pressure cuff.[7] However, since the length of exposure increases the risk of injury, these lesions are seen more frequently in patients after prolonged ventilation.

The development of the large-volume, low-pressure cuff for tracheostomy and endotracheal tubes for ventilation has greatly lowered the incidence of cuff stenoses. However, since the compliance curve of the plastic from which these cuffs are made is unsatisfactory when the cuff is inflated beyond its normal filled volume, pressure rises rapidly with additional filling. Therefore, overinflation of these cuffs converts them to high-pressure cuffs. This fact leads to a continued incidence of cuff stenosis.

Malacia of the trachea rather than stenosis may also occur at the level of cuff injury. The mucosa generally reveals squamous metaplasia in contrast to the scar tissue seen in the stenotic lesion. It is not clear why some patients develop malacic lesions rather than stenosis. Areas of malacia can also be seen between the level of a tracheal stoma and a cuff stenosis.

TEFs occur most often in patients who have an infected cuffed tube in the trachea for a long period of time concomitant with a nasogastric tube in the esophagus. These may represent large fistulas that can extend from one cartilaginous margin to the other. In most cuff fistulas, there is a circumferential injury to the trachea at the level of the fistula. Smaller fistulas are occasionally seen, which may be related to the tip of the tube pointing against the membranous wall. These variations must be considered in surgical repair.

Anterior injuries of the trachea may lead to the development of tracheoinnominate artery fistulas. These are most often due to direct erosion of the inner elbow of the tracheostomy tube in an inferiorly placed stoma. Placement of the tracheal stoma at the conventional level of the second or third tracheal ring prevents these fistulas.

Radiation therapy can produce late stenosis of the larynx and trachea. Because of the intrinsic damage to these tissues, surgical repair is hazardous. Tracheal stenosis due to irradiation may be treated with T-tube placement or carefully considered reconstruction with omental transfer to augment healing in select patients.[8]

## Idiopathic Laryngotracheal Stenosis

A minority of patients present with stenosis of the airway at various levels without history of trauma, infection, inhalation injury, or airway intubation. This diagnosis is one of exclusion and is characterized by an inflammatory cicatricial stenosis at the level of the subglottic larynx, cricoid, and upper trachea. An overwhelming majority of these patients are female and typically present with signs and symptoms of upper airway obstruction.[9] This process is confined intrinsically to the wall of the airway and the immediately surrounding connective tissue. Histology shows extensive fibrosis, acute and chronic inflammation, and dilation of mucus glands with relatively normal cartilage.[10] All patients should be screened for connective tissue disorders and Wegener's granulomatosis by serum ANA and ANCA.

It is impossible to predict the future course of the disease. The presence of active inflammation is best treated by serial dilation until the inflammatory process subsides. When airway obstruction becomes severe and does not respond for sufficiently long intervals to dilatation, surgery is indicated. Patients are best treated with definitive single-stage laryngotracheal resection and primary reconstruction.[9] The goal of reconstruction is removal of all of the scarred tissue and reconstruct with healthy tissue.

## Tracheobronchomalacia

Acquired tracheomalacia may result from postintubation injury. However, in patients with chronic obstructive pulmonary disease, malacia may develop in the lower trachea, main bronchi, and sometimes the more distal bronchi in the absence of prior intubation. When the patient attempts to expire or to cough, the membranous wall approximates to the anterior, softened cartilaginous wall, causing nearly total obstruction. Consequently, the posterior membranous wall elongates and becomes redundant. It is possible to ameliorate the deformity by pulling the ends of the cartilages toward one another posteriorly, restoring a more circular shape to the airway. The redundant membranous wall must be tacked to the posterior splinting material to prevent it from falling forward into the lumen. Various materials have been used for splinting, none with complete success. These have included fascia lata, pericardium, lyophilized bone, polytetrafluoroethylene, and rigid plastic splints. We currently use sheets of polypropylene mesh to plicate the membranous wall as described by Rainer.[11]

## Tracheal Tumors

Primary tracheal tumors are rare. It is estimated that tracheal tumors occur in about 2.7 new cases per million per year.[12] The rarity of these tumors and their often insidious presentation frequently lead to a delay in diagnosis and inappropriate treatment until the definitive diagnosis is made.

### TUMOR CLASSIFICATION

About two-thirds of primary tracheal tumors are of two histologic types: squamous cell carcinoma (SCC) and adenoid cystic carcinoma (ACC), formally known as "cylindroma." These two types occur with equal frequency. The remaining third of the tumors are widely distributed in a heterogeneous group, both malignant and benign. A variety of secondary tumors involve the trachea. These include carcinomas of the larynx, thyroid, lung, and esophagus. Rarely, tumors may metastasize to the submucosa of the trachea or to the mediastinum, with secondary invasion of the trachea. Thus, carcinoma of the breast and mediastinal lymphoma may invade the trachea.

SCC may be either exophytic or ulcerative. It may also be multiple and extend over a considerable length of trachea. The tumor metastasizes to the regional lymph nodes and, in its more aggressive and late forms, invades mediastinal structures. In general, its progress appears to be relatively rapid in comparison with that of ACC. A number of these patients have returned with a second SCC of the lung or oropharynx. SCC occurs predominantly in men, usually cigarette smokers.[13]

ACC often has an indolent course, frequently eluding diagnosis for years. Tumor recurrence may occur years after surgical resection. ACC may extend over long distances submucosally in the airways and also perineurally. It spreads to regional lymph nodes, although less frequently than SSC. Although it may invade the thyroid or muscular coats of the esophagus by contiguity, ACC frequently displaces mediastinal structures before actually invading them. Metastases to the lungs are not uncommon. These may grow very slowly over a period of years and remain asymptomatic until they become quite large. Metastases to bone and other organs can also occur. In contrast to tracheal SSC, men and women are equally affected and there is no clear association with tobacco smoke exposure.[12]

The group of tumors other than SCC and ACC, although representing only about one-quarter of the population, is composed of a multitude of tumor types and varying degrees of malignancy, including both epithelial and mesenchymal neoplasms. This list includes pleomorphic adenomas, leiomyomas, chondromas, carcinoid tumors, mucoepidermoid tumors, and sarcomas.

Secondary tumors involving the trachea should be briefly noted. Both papillary and follicular carcinoma of the thyroid and mixed varieties of the two may invade the trachea primarily, usually at the level of the isthmus.[14] Invasion of the trachea by thyroid carcinoma is best managed by resection

with airway reconstruction. Localized extension of tumor may also require partial esophageal resection or radical resection, including laryngectomy with mediastinal tracheostomy. More commonly, invasion is seen after thyroidectomy for carcinoma, in cases where surgeons were aware that they were "shaving off" the tumor from the trachea. In such cases, concurrent or early resection of the involved trachea should be considered.

## CLINICAL FEATURES

Patients with pathologic lesions of the trachea usually present with signs and symptoms of upper airway obstruction: dyspnea on exertion, wheezing, stridor, and obstructive pneumonia. The most common presentation, wheezing and dyspnea on exertion, is frequently misinterpreted as adult-onset asthma. It is not uncommon for the symptoms in these patients to become progressively worse and correspondingly be treated with corticosteroids before the correct diagnosis is finally made. It should be a diagnostic rule that any patient who presents with such symptoms and has been intubated and ventilated must be considered to have organic stenosis unless proven otherwise.

Tumors of the trachea may also present insidiously. Their most common signs and symptoms are cough (37 percent), hemoptysis (41 percent), and the signs of progressive airway obstruction, including shortness of breath on exertion (54 percent), wheezing and stridor (35 percent), and, less commonly, dysphagia or hoarseness (7 percent).[12] Signs and symptoms may vary with the histology of the tumor. Hemoptysis is prominent in patients with SSC and usually leads to earlier diagnosis. ACC more commonly presents with wheezing or stridor as a predominant symptom, often leading to delay in diagnosis. In one study, the mean duration of symptoms prior to diagnosis in patients with SCC of the trachea was only 4 months, whereas in those with ACC, it was 18 months.[15]

Among nonintubated patients, TEF is manifest by episodes of choking while swallowing, suctioning of food or beverage from trachea, or an increase in tracheal secretions. Among intubated patients, there may be gastric distention or loss of delivered tidal volume. Tracheoinnominate arterial fistulas are rare but may be announced by a premonitory hemorrhage. In treating bleeding from a tracheostomy, it is important to differentiate between erosion of tracheal granulations or mucosa and arterial fistula. Any suspicious hemorrhage from a tracheal stoma should be immediately investigated.

## DIAGNOSTIC MODALITIES

### Radiographic Assessment

Definitive diagnosis of airway problems is often delayed because of an apparently normal chest radiograph. Closer inspection will often reveal abnormality of the tracheal air column. Lesions can frequently be seen on overpenetrated views or tomograms of the larynx and trachea. The location of the lesion, its linear extent, extratracheal involvement, and the amount of airway uninvolved can be determined. Lateral neck views, using soft tissue technique with the patient swallowing and the neck hyperextended to bring the trachea up above the clavicles, are useful to define pathology in the upper trachea. Fluoroscopy not only demonstrates functional asymmetry of the vocal cords if present but may also give additional information about the extent of the lesion and collapse of the airway if malacia is present. In some cases, polytomography (AP and lateral views) gives additional detail, particularly of mediastinal involvement. Computed tomography (CT) offers little overstandard radiologic techniques for benign disease but is especially helpful in malignant disease to assess extramural extent and enlarged lymph nodes. A combination of inspiratory and expiratory images from a CT is currently the easiest and most accurate noninvasive method of diagnosing tracheomalacia.[16] The exact role of magnetic resonance imaging (MRI) is yet to be defined. Sagittal and coronal views, however, have been helpful in certain cases and may provide more accurate detail than standard radiographic techniques.

### Bronchoscopy

Certainly the role of both flexible and rigid bronchoscopy in the diagnosis of tracheal pathology cannot be overstated. Biopsy specimens of both benign and malignant lesions of the trachea are made with these techniques. In planning surgical resections, bronchoscopy is invaluable. Definitive assessment of the airway is performed by meticulous endoscopic measurements with a rigid bronchoscope. Measurement of the carina, bottom of the lesion, top of the lesion, and level of the vocal cords will determine the extent of the disease process and likelihood of reconstruction. At the time of bronchoscopy, it is important to assess the adequacy of the larynx and degree of inflammation of the mucosa.

#### AIRWAY MANAGEMENT AND ENDOSCOPY

Crucial to the management of all problems of the trachea is the ability to control the airway. Tracheal trauma, tumors, and postintubation stenosis may present with acute airway obstruction. Endotracheal intubation may be impossible and even dangerous, especially in patients with high tracheal lesions. Simple maneuvers to elevate the head of the patient, administration of cool mist, oxygen, and careful sedation may allow control of the airway to be accomplished in a semielective manner. Control is best accomplished in the operating room, where an assortment of rigid bronchoscopes, dilators, biopsy forceps, and instruments to perform emergency tracheostomy are available. Anesthesia, as in elective tracheal operations, is best accomplished by inhalation technique

to allow spontaneous ventilation.[17] Muscle-relaxing agents should not be used to avoid the lethal combination of airway obstruction and an apneic patient.

Initial evaluation should be performed with a rigid bronchoscope carefully inserted through the vocal cords, stopping just proximal to the level of obstruction. This can be passed beyond most tumors, even those causing nearly total obstruction. Once the status of the distal airway has been assessed, the tumor can be partially removed with biopsy forceps to determine its consistency and vascularity. For most tumors, the tip of the rigid bronchoscope can be used to core out most of the tumor.[17] The tumor can then be grasped with biopsy forceps and removed. If bleeding ensues, the bronchoscope may be passed into the distal airway for ventilation, and this will also serve to tamponade bleeding.

Postintubation stenoses pose a slightly different problem in airway control. Bronchoscopy is invaluable in determining the extent of airway involvement and, just as importantly, the amount of uninvolved airway. Measurements as accurate as possible should be recorded. The quality of the mucosa should be carefully assessed. Marked inflammation and erythema may dictate delay of definitive surgical correction to a time when this has subsided. Both flexible and rigid bronchoscopes are used in these situations.

Caution must be taken with flexible bronchoscopy in the assessment of critical airway stenosis. The flexible bronchoscope may precipitate airway obstruction in patients with critical stenoses by increasing secretions or causing bleeding or edema. If the physician performing the endoscopy is unprepared to dilate the patient emergently, lethal airway obstruction may occur. Whenever severe airway stenosis is encountered, it is best not to manipulate the stenosis with the flexible bronchoscope. Proper evaluation should be performed in the operating room with facilities available to dilate the stenosis if necessary. In nonemergent cases, endoscopy is best performed as part of the planned surgical procedure.

As a general rule, the rigid bronchoscope is much more valuable in assessing airway pathology. Attempting to pass a large rigid bronchoscope beyond a tough, inflammatory stricture may be impossible, may result in tracheal rupture, or may cause total airway obstruction secondary to bleeding or edema. Jackson dilators passed through the rigid bronchoscope under direct vision and an assortment of graduated rigid bronchoscopes can be used to serially dilate postintubation and idiopathic strictures. By gradually dilating these tight, rigid strictures, the risk of perforation and bleeding is minimized. Racemic epinephrine and steroids are often used for 24 to 48 h to minimize subsequent reactive edema.

It is important to understand that dilation or endoscopic removal of malignant or inflammatory strictures is often only a temporizing measure. In the case of inflammatory stricture, restenosis usually develops within days to weeks. The use of these techniques in emergent situations allows more thorough evaluation of the patient and enables surgery to be performed electively. Many patients are on corticosteroids at the time of presentation and, by improving the airway, these may be tapered and discontinued. This will enable the operation to be performed at a later time without the threat of impaired healing.

The above maneuvers are also used in an elective operation when the patient has presented with a narrowed but not critical airway. Dilation with rigid bronchoscopy permits assessment of the distal airway, placement of an endotracheal tube, and provision of an adequate lumen to prevent carbon dioxide accumulation early in the procedure.

Tracheostomy may be necessary in some patients as the only method to secure an airway. If feasible, this should be placed through the most damaged portion of the trachea to preserve the maximal amount of normal trachea for subsequent reconstruction. If tracheostomy is contemplated at the completion of tracheal resection, which is rarely necessary, it should be placed at least two rings away from the anastomosis. The anastomosis should then be protected with the thyroid gland or strap muscles to avoid contamination of the suture line. This will lessen the likelihood of subsequent dehiscence or stenosis. A tracheostomy tube should never be placed through an anastomosis.

## Surgical Therapy

### ANESTHESIA

Anesthesia for tracheal reconstruction, especially where there is a high degree of airway obstruction distally, is best administered by inhalational agents.[17] A slow, patient induction may be necessary if there is a high degree of airway obstruction. This is preferable and safer than paralysis of respiration with a consequent urgent need to establish an airway.

The surgeon should be available with an array of rigid bronchoscopes from pediatric to adult sizes as the induction commences. The residual airway through which the patient is breathing may measure as little as 2 or 3 mm in diameter. In most cases, tumors are not circumferential. After bronchoscopy, a small endotracheal tube can often be insinuated past a highly obstructive tumor. In other cases, the tube is left above the tumor. This contrasts with the circumferential stenoses seen in some inflammatory lesions. In rare cases, it may be necessary to resect portions of tumor with biopsy forceps to enlarge the channel for passage of a tube.

At the time of tracheal division, this tube is pulled back or removed and a sterile cuffed, flexible, and armored endotracheal tube is inserted into the distal airway across the operative field. Sterile connecting tubing is passed to the anesthesiologist to allow ventilation of the patient. This armored tube is removed whenever necessary for suctioning or placement of sutures. Toward the completion of the operation, the original endotracheal tube is advanced into the distal airway and the anastomotic sutures are tied. The patient should be breathing spontaneously at the end of the procedure so that extubation can be performed in the operating room. High-frequency ventilation has been used

with equal success intraoperatively, but we have been quite satisfied with the technique described. High-frequency ventilation is especially useful in certain complex carinal reconstructions.

Ideally, the patient should be extubated and breathe spontaneously at the conclusion of the procedure. Particularly where the trachea has been greatly shortened, it is desirable not to have even a low-pressure cuff lying in contact with the anastomosis for any period of time. The use of cardiopulmonary bypass is not usually necessary in adult tracheal surgery, even in complex carinal reconstructions. However, it may be requisite in repairing congenital airway lesions in the pediatric population, especially in the presence and correction of cardiac anomalies.[18]

## Maneuvers to Minimize Tension

Most tracheal operations can be performed without complex tracheal release maneuvers. The location of the lesion is an important factor in determining which procedures will be of benefit. Certain maneuvers are more effective for achieving additional length in performing surgery for disease in the cervical trachea, whereas others are more effective for the intrathoracic trachea. A release maneuver is primarily performed to prevent unnecessary tension on the anastomosis and avoid the need for excessive dissection of the trachea, which might jeopardize the lateral blood supply.

The simplest maneuver to minimize tension after tracheal resection for cervical pathology is flexion of the neck and mobilization of the pretracheal plane, avoiding the lateral blood supply to the trachea. Flexion of the neck between 15 and 35 degrees may result in downward movement of the trachea by as much as 4.5 cm, or the equivalent of seven tracheal rings. Flexion beyond this may achieve up to 1.5 cm of added length. The amount of trachea that may be removed with simple flexion varies greatly with the patient's age and physical habitus as well as other conditions. When these simple maneuvers fail to provide sufficient length, a Montgomery suprahyoid laryngeal release can be performed, generally before the anastomosis is completed.[19] This is accomplished by dividing the muscles that insert on the superior aspect of the hyoid bone. The hyoid bone is then divided just medial to the lesser cornua. When this maneuver is performed, an additional 1.5 cm of length can be obtained.

Flexion of the head and mobilization of the anterior surface of the trachea is also important for lower tracheal lesions. Laryngeal release has not been helpful in gaining additional length for intrathoracic tracheal lesions. Mobilization of the right hilum and inferior pulmonary ligament should be completed first. A U-shaped incision in the pericardium below the inferior pulmonary vein will allow the hilar structures and bronchus to advance in a cephalad fashion.[20] Additional length may be obtained by completely incising the pericardium around the hilar vessels.

## Tracheal Resection

### CERVICAL APPROACH

The cervical or upper cervicomediastinal approach is used for limited tumors of the upper trachea and for almost all benign strictures of the trachea at any level. The patient is usually anesthetized by inhalation and a rigid bronchoscope is passed. A stricture less than 6 mm in diameter is dilated under direct vision with rigid pediatric bronchoscopes. If the stricture is greater than 6 mm in diameter, an endotracheal tube may be placed just above the lesion. If the lesion is subglottic, the stricture must be dilated and a small endotracheal tube passed through it. An endotracheal tube may be slipped past most tumors or through the cored center of the rare circumferential tumor. If jet ventilation is employed, a tube as small as 14F suffices.

The trachea is explored through a collar incision, which may circumcise an existing tracheal stoma (Fig. 8-4A). The anterior surface of the trachea is exposed from the cricoid cartilage to the carina. The thyroid isthmus is then divided, dissected from the trachea, and retracted laterally with sutures. In inflammatory lesions, it is essential to keep the dissection close against the trachea to avoid the risk of injury to the back wall of the innominate artery. If the lesion extends below the sternal notch, making it easily accessible through the collar incision, the exposure is increased by making a "T" incision with the vertical arm extending downward to a point 1 cm below the sternal angle (Fig. 8-4B). The sternum is divided to that point only and is separated with a small chest spreader. Exposure is not improved with a full median sternotomy, since the carina lies at the level of the angle of Louis, and the great vessels, lying anteriorly, inhibit better visualization.

In cases of inflammatory stenosis, meticulous dissection is performed along the lateral aspects of only the involved trachea. If there is difficulty in identifying the level of the lesion, intraoperative bronchoscopy will facilitate its recognition. The position of the bronchoscope light is identified at the upper and then the lower extent of the lesion while an assistant pushes a #25 needle through the tracheal wall for precise localization. Dissection close to the tracheal wall or the scar replacing it avoids injury to the recurrent laryngeal nerves, which lie in the tracheoesophageal groove on either side. The nerves are intentionally not exposed. This is a particularly important point if the stenosis is located just below the cricoid cartilage, since the recurrent nerves enter the larynx just medial to the inferior cornua of the thyroid cartilages.

The trachea is then circumferentially dissected at the level immediately below the distal margin of the lesion (Fig. 8-4C). Sterile anesthesia equipment is assembled on the field prior to division of the trachea. Lateral traction sutures of 2-0 Vicryl are placed on either side of the trachea in the midlateral portion approximately 1 cm below the anticipated level of transection. These pass vertically through the full thickness of the tracheal wall and around one or more rings (Fig. 8-5A). The trachea is opened anteriorly just distal to the lesion, staying close to the lesion if it is benign. If the

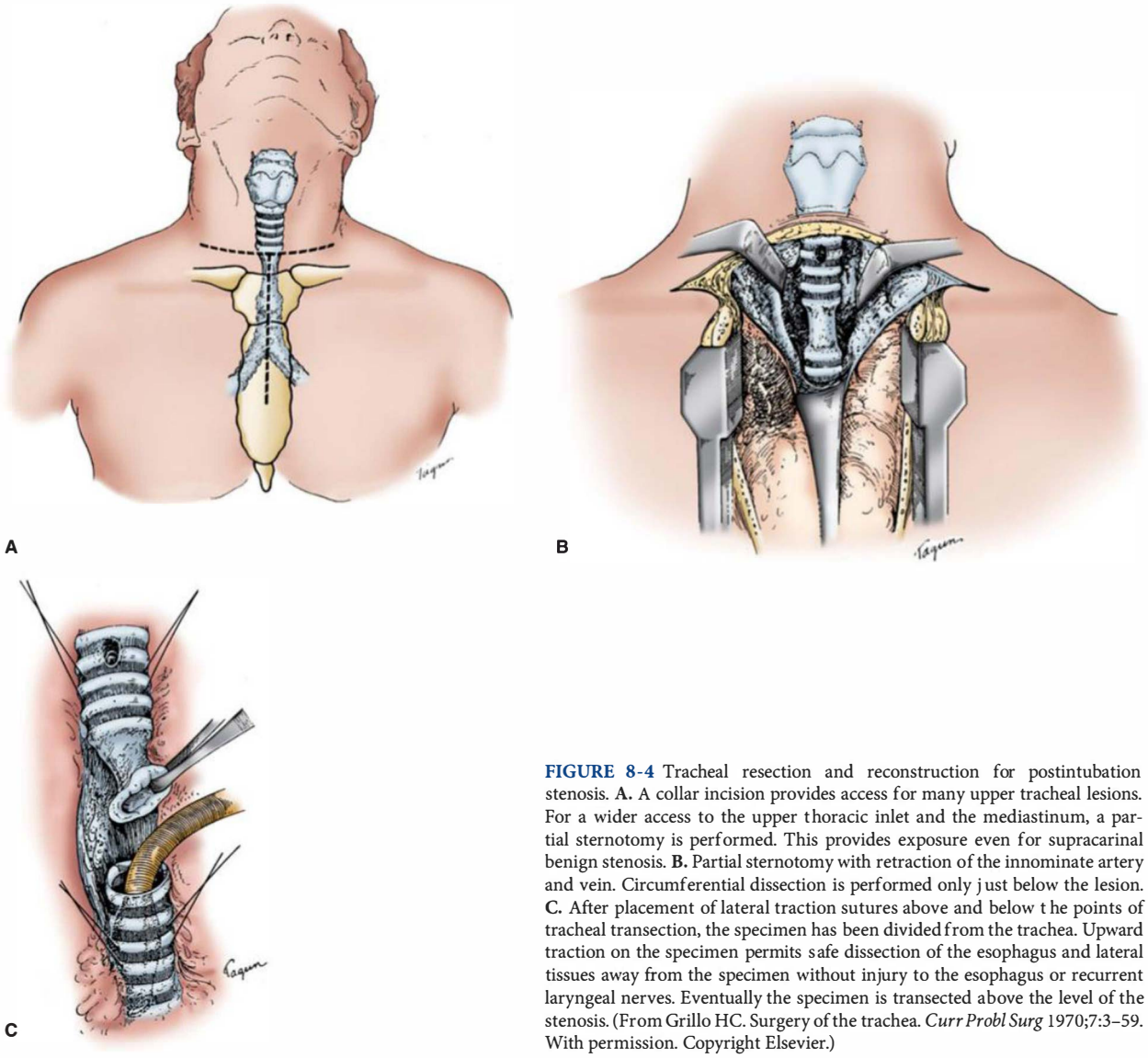


**FIGURE 8-4** Tracheal resection and reconstruction for postintubation stenosis. **A.** A collar incision provides access for many upper tracheal lesions. For a wider access to the upper thoracic inlet and the mediastinum, a partial sternotomy is performed. This provides exposure even for supracarinal benign stenosis. **B.** Partial sternotomy with retraction of the innominate artery and vein. Circumferential dissection is performed only just below the lesion. **C.** After placement of lateral traction sutures above and below the points of tracheal transection, the specimen has been divided from the trachea. Upward traction on the specimen permits safe dissection of the esophagus and lateral tissues away from the specimen without injury to the esophagus or recurrent laryngeal nerves. Eventually the specimen is transected above the level of the stenosis. (From Grillo HC. Surgery of the trachea. *Curr Probl Surg* 1970;7:3–59. With permission. Copyright Elsevier.)

wall is still diseased at this point, a second incision is made one ring lower until good tissue is identified; then the trachea is transected. After the transection, an assistant maintains tension on the two lateral traction sutures and holds the flexible armored ventilating tube in the distal trachea. Circumferential dissection of the residual distal trachea is limited to its first 1 to 2 cm to protect the segmental blood supply. Devascularization invites necrosis and a possibly irreparable restenosis.

In the case of tumors of the upper trachea, since there is no peritracheal inflammation, the recurrent laryngeal nerves are usually identified and followed to above the level chosen for tracheal transection. This permits excision of paratracheal lymph nodes immediately adjacent to the tumor-bearing segment. To determine the appropriate level of tracheal transection, the trachea is initially opened through a tumor-free area at the level of the tumor.

Lateral traction sutures are placed proximally 1 cm above the proposed proximal level of transection. Again, no more than 1 cm of trachea is freed circumferentially. If the upper level of transection is at the inferior border of the cricoid cartilage, no attempt is made to dissect more cephalad posteriorly, since this would involve the zone of fusion between the upper esophagus and the cricoid, risking esophageal injury. To test the ease with which the tracheal ends can be brought together, the anesthetist flexes the patient's neck and

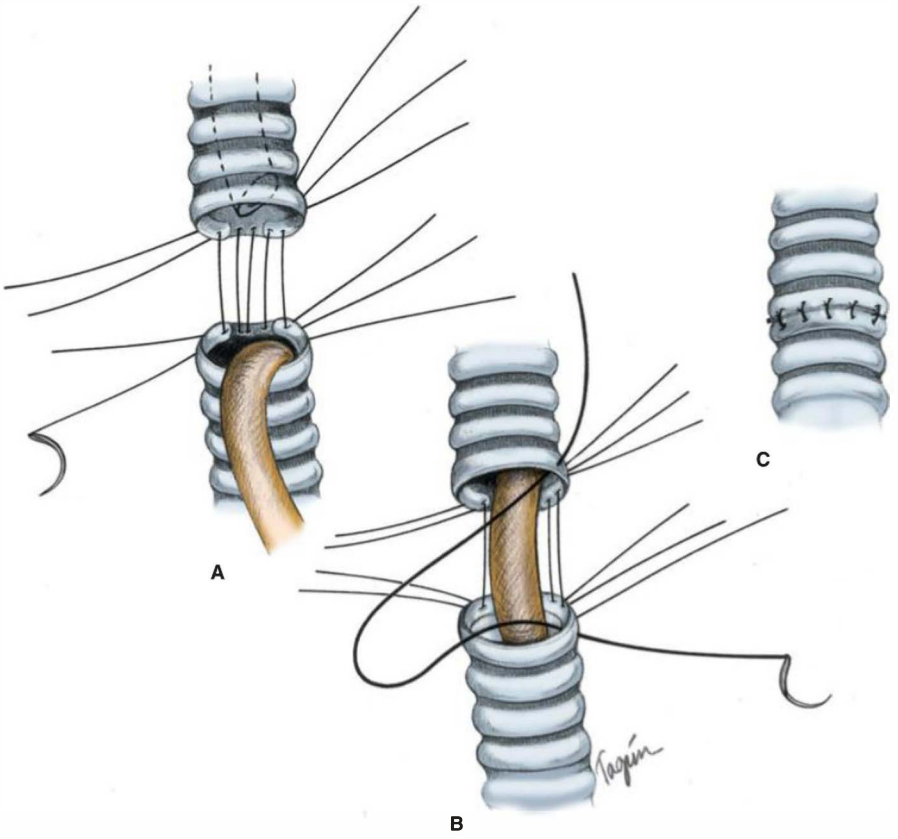



**FIGURE 8-5** **A.** Tracheal anastomosis. Sutures are placed individually, beginning in the midline posteriorly and ranging anteriorly on either side. **B.** After the sutures have been placed on either side up to the level of the midlateral traction sutures, the anterior sutures are placed. Frequently, the endotracheal tube is not advanced from above until after all sutures have been placed. **C.** The neck is placed in the flexed position and the lateral traction sutures are tied on either side (not shown) to remove tension from the anastomotic sutures. After this, anastomotic sutures are tied from anterior to posterior on either side. The completed anastomosis is airtight. (From Grillo HC. Surgery of the trachea. *Curr Probl Surg* 1970;7:3–59. With permission. Copyright Elsevier.)

the proximal and distal traction sutures are crossed, bringing the tracheal ends together. Importantly, the length of trachea that may be safely removed must be determined prior to division. Whether resection is feasible is usually based on radiologic and bronchoscopic measurements made prior to skin incision and rarely on surgical exploration.

Once it has been demonstrated that the anastomosis can be performed without excessive tension, the neck is again hyperextended. The first anastomotic suture—we prefer 4-0 coated Vicryl—is placed in the posterior midline with the knots outside, and the suture is clipped to the drapes above. The next suture is placed lateral to this and clipped to the drapes just caudad to the previous one. The sutures are thus serially inserted until a point is reached just posterior to the midlateral tracheal traction suture (Fig. 8-5A). The same placement of sutures is now carried out on the opposite side, from the posterior midline to the midlateral suture. Serial sutures are placed anteriorly, proceeding from the lateral traction sutures to the midline (Fig. 8-5B). The cross-field ventilatory tube may have to be removed intermittently for the placement of difficult sutures or drawn to one side as the sutures are inserted.

When all sutures have been placed, the oral endotracheal tube is advanced from above until the end is visible in the wound. The distal trachea is suctioned, the tube in it is withdrawn, and anesthesia is now resumed via the original endotracheal tube, which is advanced into the distal trachea beyond the anastomosis. The patient's head is firmly supported on blankets in full flexion and then the lateral traction sutures are crossed, pulled together on either side, and tied. The tracheal ends are apposed end-to-end, not deliberately intussuscepted.

The anterior anastomotic sutures are tied first, without tension, and the ends are cut after tying each. The assistant now rotates the trachea by gently drawing medially on the traction sutures on the surgeon's side of the table. The suture just posterior to the lateral traction suture is tied, as then are the rest of the posterior sutures. This is then repeated on the opposite side (Fig. 8-5C). The ends of

traction sutures are removed, leaving their knotted loops in place to guard against tension on the anastomotic sutures. The integrity of the anastomosis is checked under saline. Flat, closed suction drains are placed in the pretracheal and substernal spaces, and the strap muscles are approximated in the midline.

After the incision has been closed, a heavy suture is placed through the skin crease beneath the chin and through the presternal skin. Two sutures, one on each side, may be used if a midline incision was necessary. These sutures are tied with the patient's neck in flexion to guard against sudden hyperextension of the neck in the first week following operation.

The patient is usually extubated in the operating room. An unsatisfactory airway at this point is not likely to improve unless the problem is secondary to laryngeal edema. If this is the case, a small endotracheal tube can be left in position until the problem subsides. It is preferable to leave the cuff deflated if possible.

### TRANSTHORACIC APPROACH

The transthoracic approach using a posterolateral thoracotomy through the fourth intercostal space is used for tumors of the lower trachea and carina and for a few inflammatory lesions. The right arm is draped free, and the neck and anterior chest are included in the field. This allows for alteration of the incision or the addition of a cervical component should laryngeal release or other maneuvers may be necessary. An extra long, single-lumen endotracheal tube with sufficient diameter is used to intubate a main bronchus.

Dissection of the thoracic trachea is carried out in a similar fashion to that for more proximal pathology. In cases of malignancy, an effort is made to resect surrounding tissues with the tumor. Eventually, the trachea is dissected circumferentially below the tumor and sometimes above it, although the upper portion of the dissection can be completed after division of the trachea below. Traction sutures are placed in the midlateral tracheal wall distal to the tumor. If the transection is close to the carina, the sutures are placed in the lateral walls of the right and left main bronchi. Again, anesthesia tubing brought across the field is joined to a flexible armored tube placed in the distal trachea or, preferably, the left main bronchus to allow collapse of the right lung for better exposure during the anastomosis. If this results in significant intrapulmonary shunting, the right pulmonary artery may be gently clamped.

Flexion of the neck, even with the patient in the lateral thoracotomy position, delivers the proximal trachea into the thorax. Dissection anterior to the trachea and both main bronchi will provide additional mobility. These are important maneuvers in obtaining a tension-free anastomosis. In the resection of a malignant tumor, paratracheal and subcarinal lymph nodes that are not in proximity to the mass should not be radically resected for fear of devascularizing the airway. The technique of anastomosis is similar to that used in the upper trachea.

## Laryngotracheal Trauma

The laryngotracheal junction is the most frequent location of injury in airway trauma. The most important initial aspect of treating a laryngotracheal injury is the establishment and maintenance of an airway. The wound is debrided and those familiar with the techniques of tracheal repair may directly anastomose the trachea. If the surgeon lacks experience or if other life-threatening injuries demand, it is preferable to anchor the distal trachea to the base of the neck and place a tracheostomy tube in the distal separated end. In this case, distal tracheostomy should not be done, as it will only further injure tracheal tissue and provide no advantage over a tube placed in the already divided end. Secondary repair can be performed at a later date. If tracheal repair is performed, it will be necessary in most cases to place a small protective tracheostomy approximately 2 cm below the anastomosis. This serves to compensate for severely impaired glottic function due to concurrent injuries to the recurrent laryngeal nerve.

Traumatic lacerations of the lower trachea can often be repaired through an anterior approach. This can be achieved either through a partial sternotomy or, if addressing cardiac injuries, through a full sternotomy with additional exposure obtained using anterior and posterior pericardiotomies between the superior vena cava and aorta. For those less familiar with this approach, the lowermost trachea as well as carinal and bronchial ruptures are best approached through a right posterolateral thoracotomy.

## Slide Tracheoplasty

Three surgical techniques have been described for correction of congenital tracheal stenoses. First, tracheal resection and reconstruction in children has been described.[21] This has limited utility in the pediatric population, as only a finite length of trachea, approximately 25 to 30 percent, can be resected and followed by end-to-end suture before excessive anastomotic tension may result in separation.[22] To address this issue, patients with long congenital stenoses have been treated with an anterior tracheoplasty and patch repair with costal cartilage or pericardium.[23] The latter must be suspended to the mediastinum, and all patch techniques require prolonged stenting with intubation during early healing. This approach has also been complicated by the formation of excessive granulation tissue arising from the mesenchymal surface of the patches, often requiring multiple bronchoscopic debridements. These patches can also suffer from necrosis and/or collapse, necessitating reoperation. Goldstraw introduced slide tracheoplasty as an alternative to the management of patients with long-segment congenital tracheal stenosis.[24]

The surgical approach for these lesions is similar to that used for tracheal pathology in adults. The upper and lower ends of the stenotic segment are precisely identified, so that the lesion might be divided horizontally at its midpoint (Fig. 8-6A). Dissection is carried circumferentially around

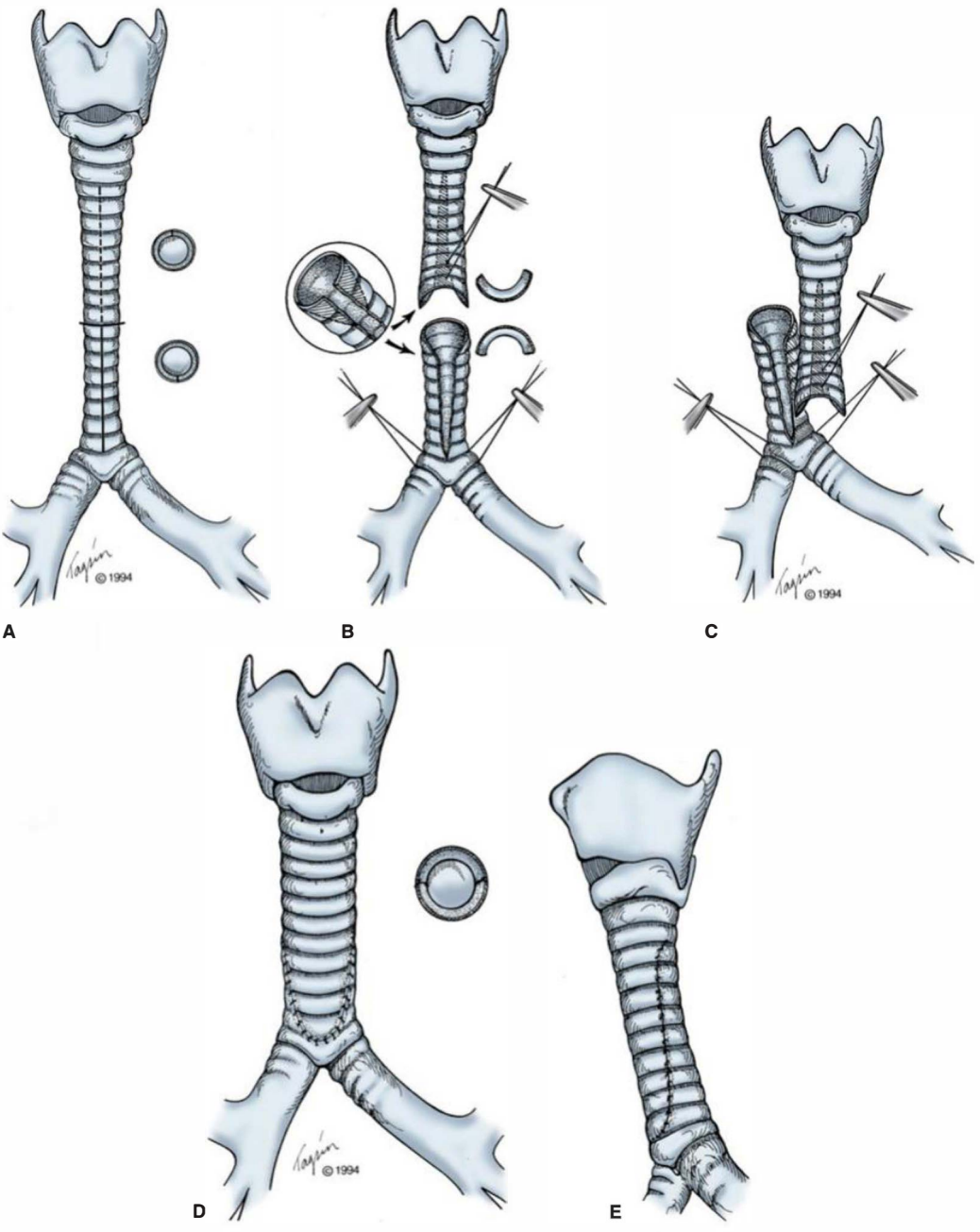



**FIGURE 8-6** Technique of slide tracheoplasty. **A.** The extent of stenosis is precisely identified. The stenotic segment is divided transversely in its midpoint after circumferential dissection at that locus only. The upper stenotic segment is incised vertically posteriorly, and the lower segment is incised anteriorly for the full length of stenosis. **B.** The right-angled corners produced by these divisions are trimmed above and below. A stay suture near the tip of the superior flap and traction sutures at the tracheobronchial angles or main bronchi are both helpful. Minimal dissection of lateral blood supply is performed. **C.** The two ends are pulled together after placement of individual anastomotic sutures around the entire oblique circumference of the tracheoplasty. **D** and **E.** The circumference is doubled, resulting in a fourfold increase in cross-sectional area. (From Grillo HC. Slide tracheoplasty for long segment tracheal congenital stenosis. *Ann Thorac Surg* 1994;59:613–621. Reprinted by permission from the Society of Thoracic Surgeons.)

the midpoint of the stenotic segment only. It is helpful to place traction sutures of 3-0 Vicryl in the midlateral point of the tracheobronchial junction on either side or in the proximal right and left main bronchi (Fig. 8-6B). Following transection of the trachea, intubation and ventilation are carried out across the operative field.

Vertical divisions of the proximal and distal segments are next carried out (Fig. 8-6B and C). It is essential that the full length of stenosis be incised. The right-angled corners of tracheal wall represented by the meeting points of the vertical and horizontal incisions are trimmed to make a gently sloping corner (Fig. 8-6D). The lateral blood supply is hardly disturbed for the lower segment, as the vertical incision is based anteriorly. For the upper segment, however, somewhat more circumferential dissection is necessary. A single 3-0 Vicryl suture is placed through and through the tracheal wall close to the distal tip of the upper flap for traction (Fig. 8-6C). The anastomosis is created using techniques similar to those described earlier (Fig. 8-6D and E).

## Tracheoesophageal Fistulas

We have proposed a conservative approach to the management of acquired, nonmalignant TEFs.[25] As stated previously, the majority of these result from complications of mechanical ventilation and most are actually diagnosed while patients are being mechanically ventilated. This important fact dictates our approach to this problem.

It is known from our experience with tracheal reconstruction for postintubation tracheal stenosis that postoperative mechanical ventilation is associated with a higher incidence of anastomotic complications.[26] Most TEFs require tracheal resection because of circumferential injury to the trachea or size of the fistula. We have therefore adopted an approach that delays definitive correction of the fistula until patients have been successfully weaned from mechanical ventilation.

The devastating pulmonary complications from TEFs can be minimized by a few simple maneuvers. A new tracheostomy tube should be placed so that the balloon is below the fistula, so as to minimize soiling of the tracheobronchial tree. A draining gastrostomy tube should be placed to minimize gastroesophageal reflux, and a feeding jejunostomy tube should be placed for nutritional supplementation. These measures should obviate the need for esophageal diversion and ligation of the gastroesophageal junction. Esophageal diversion should be reserved for continued soilage of the tracheobronchial tree despite the previously mentioned measures or for supracarinal fistulas that cannot be controlled otherwise. Once the patient is weaned from mechanical ventilation, single-stage repair can be undertaken without the risks of postoperative ventilation.

The principles of tracheal surgery must be closely followed, since many of these cases are reoperations or associated with more than the usual amount of inflammation. The most important initial decision is to determine whether the fistula can be simply resected and closed or whether tracheal resection and reconstruction will be required.

Most TEFs are approached through a low collar incision often including the tracheostomy stoma, if present. A right lateral thoracotomy through the fourth interspace is preferable for fistulas at or just above the carina or in the case of a reoperation if the previous procedure was performed through the chest.

The small TEF that does not require tracheal resection poses unique technical problems (Fig. 8-7A). Care must be taken to avoid injury to the recurrent laryngeal nerves, as local inflammation may make their identification difficult. In these circumstances, it is best to identify the nerves at a location remote from the fistula. The nerves should be elevated with the trachea during exposure of the fistula.

Once the fistula is identified, it should be divided. We prefer to close the tracheal defect with absorbable suture material (4-0 Vicryl). The esophageal defect is then closed in two layers (Fig. 8-7B). A local strap muscle is mobilized to buttress and separate the tracheal and esophageal suture lines (Fig. 8-7C). This should minimize the risk of recurrent fistula.

The fistula that requires tracheal resection, although technically more complicated, provides significantly improved exposure. Circumferential dissection above and below the fistula should be very close to the trachea to avoid injury to the recurrent nerves. Resection of the damaged portion of the trachea gives excellent exposure of the esophageal defect (Fig. 8-8A). The esophageal defect is closed longitudinally in two layers (Fig. 8-8B). It is essential to separate the esophageal suture line with a local strap muscle to help prevent recurrent TEF (Fig. 8-8C). Tracheal reconstruction is performed as detailed earlier (Fig. 8-8D).

## Idiopathic Laryngotracheal Stenosis

Inflammatory stenosis of the upper trachea, which also involves the subglottic larynx, cannot be treated by simple circumferential resection, since this would destroy the function of the recurrent laryngeal nerves. Many complex and multistaged procedures have been devised to solve this problem. In an effort to improve the results obtained by such operations, single-stage procedures involving partial resection of the subglottic larynx and immediate plastic reconstruction by varying techniques have evolved yielding good results. In those patients in whom the stenotic process involves only the anterior portion of the subglottic larynx, resection of this portion of the cricoid arch is sufficient (Fig. 8-9). The posterior margin of resection is along the lower border of the cricoid cartilage.

In patients with circumferential subglottic lesions extending in front of the posterior plate of the cricoid,

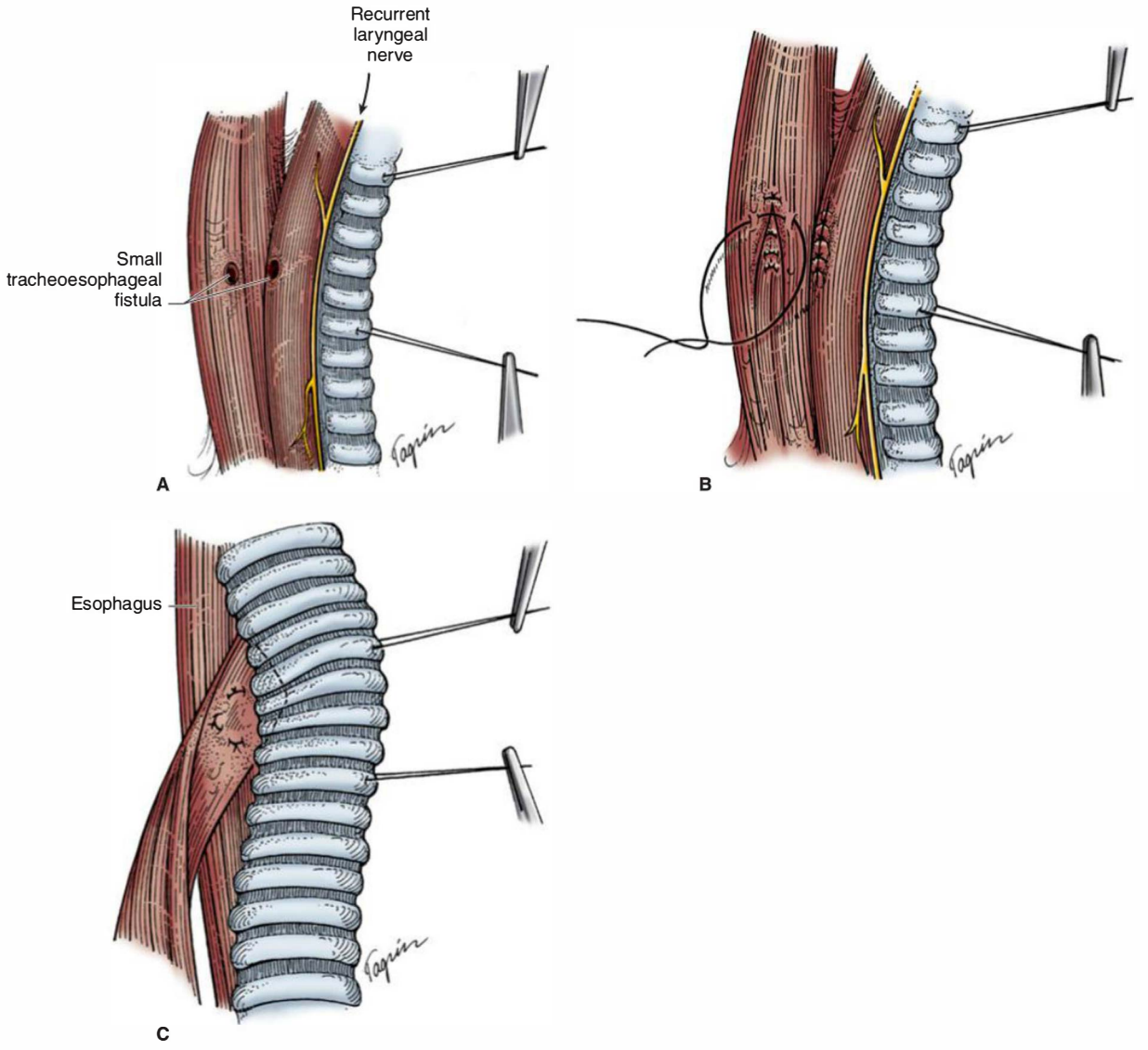



**FIGURE 8-7** **A** and **B.** Small tracheoesophageal fistula treated by division and local repair. The recurrent laryngeal nerve is elevated with the trachea. The esophagus is closed in two layers. **C.** A strap muscle is used to cover the esophageal suture line and separate it from the tracheal suture line. (From Mathisen DJ, Grillo HC, Wain JC, Hilgenberg AD. Management of acquired nonmalignant tracheoesophageal fistula. *Ann Thorac Surg* 1991;52:759–765. Reprinted with permission from the Society of Thoracic Surgeons.)

the line of posterior mucosal resection is incised above the level of stenosis, approaching the arytenoid cartilages (Fig. 8-10A). All involved mucosa and scar tissue is excised from the front of the posterior cricoid plate, leaving the cartilage intact posteriorly to be surfaced by a broad-based flap of membranous trachea advanced from below (Fig. 8-10B). The posterior cricoid plate itself is usually not significantly involved. The plane between mucosa and cartilage can be dissected with a scalpel or bluntly with a fine dental spatula. One must stop short of the superior border of the cricoid plate, which lies immediately below the arytenoid cartilages. No attempt is made to groove or otherwise alter the posterior cricoid cartilage itself. Division of the trachea is also carried out differently. Posteriorly, a flap of membranous wall is fashioned (Fig. 8-10C). When the anastomosis is made, the posterior mucosal sutures pass only through the full thickness of mucosa and submucosa of the posterior wall of the larynx and then through the full thickness of the membranous wall of the trachea (Fig. 8-10D).

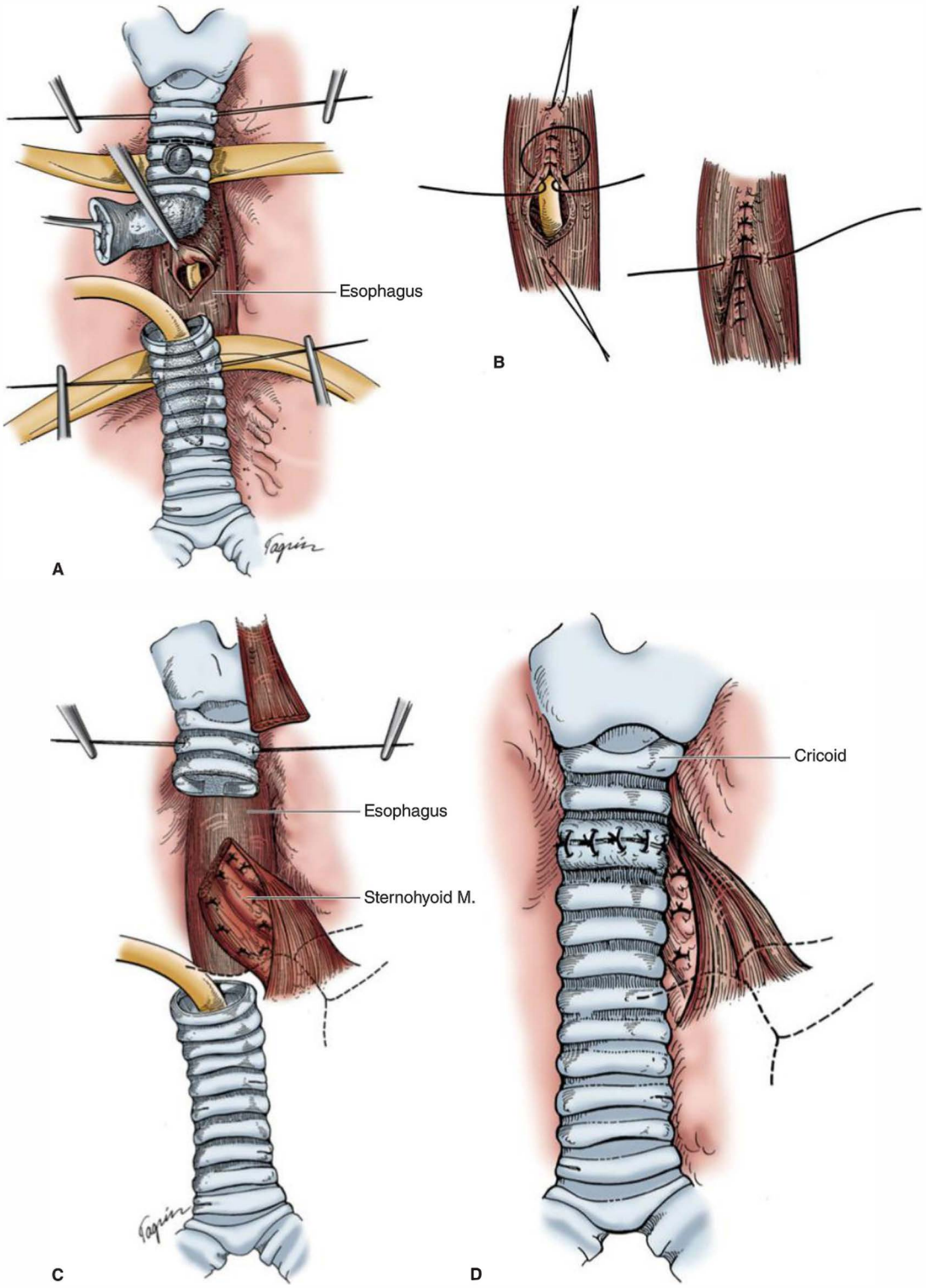



**FIGURE 8-8** **A.** Circumferential dissection above and below the fistula is near the trachea to avoid injury to the recurrent nerves. Division of damaged trachea gives excellent exposure to the esophageal defect. **B.** The esophageal defect is closed in two layers. **C.** A local strap muscle is used to buttress the esophageal closure and separate it from the tracheal suture line. M, muscle. **D.** Completed tracheal anastomosis, with strap muscle posterior to it separating it from the esophageal suture line. (From Mathisen DJ, Grillo HC, Wain JC, Hilgenberg AD. Management of acquired nonmalignant tracheoesophageal fistula. *Ann Thorac Surg* 1991;52:759–765. Reprinted with permission from the Society of Thoracic Surgeons.)

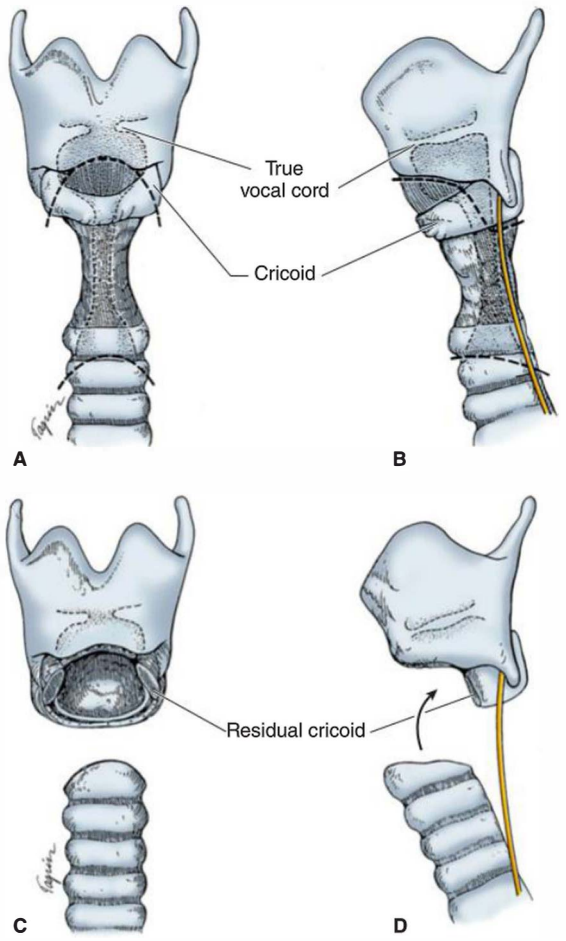



**FIGURE 8-9** Operative repair of anterolateral stenosis of the subglottic larynx and upper trachea. **A.** Anteroposterior view. **B.** Lateral view. The figures demonstrate the extent of stenosis and ultimate lines of transection. The stenosis extends into the subglottic larynx well above the border of the cricoid anteriorly. There is, however, no involvement of the posterior mucosal wall of the subglottic larynx or of the upper trachea. The proximal line of transection is centered in the midline to divide the larynx from the trachea posteriorly at the lower border of the posterior cricoid lamina or cricoid plate. Inferiorly, the most proximal tracheal ring of residual trachea is cut backward to posterior ends. **C** and **D.** Larynx and trachea after removal of the specimen. The recurrent laryngeal nerves have been left intact but are not dissected out, as might be suggested by the diagrammatic representation. The mucous membrane of the larynx has been transected sharply at the same level of division as the cartilage.

The margin of the anterior defect in the subglottic larynx is sutured in both types of resection to a prow-shaped segment of one distal tracheal ring (Fig. 8-9D). The midline of the thyroid cartilage is approximated to the midline of the peak of the most proximal cartilage of the trachea. The traction sutures are tied and followed by the individual anastomotic sutures.

# RESULTS

## Congenital Stenosis

We have generally followed a conservative therapeutic approach to airway lesions in infants and small children. As indicated earlier, the juvenile trachea tolerates anastomotic tension less well than the adult. Furthermore, following anastomosis, a small amount of edema in a small airway may cause more significant obstruction than a similar thickness of edema in the adult. While growth of a stenosis is in general proportional to that of the normal tissues and does not actually correct congenital stenosis, sufficient improvement may obviate the need for correction or permit the patient to grow, so that surgical reconstruction can be performed with less risk. As described earlier, most cases of congenital tracheal stenosis are best addressed with slide tracheoplasty.

On completion of this procedure, the circumference of the trachea is doubled, the cross-sectional area is quadrupled, and the stenotic segment is shortened by half. It is clearly advantageous to have the trachea repaired with the tracheal wall containing native cartilages and normal tracheal epithelium. It has been demonstrated that this repair provides a permanent enlargement of the airway diameter and does not inhibit subsequent tracheal growth.

Since the introduction of slide tracheoplasty at the Massachusetts General Hospital in 1991, we have treated eight patients ranging in age from 10 days to 19 years with stenoses varying in length and location as well as other associated congenital lesions.[27] All patients survived and obtained a widely patent and stable airway. In all juvenile patients, the repaired tracheal segment continued to grow. Given the intolerance of tension in juvenile tracheal anastomosis, slide tracheoplasty should, in our opinion, be considered for all but the shortest stenotic segments.

## Posttraumatic Stenosis

Earlier we published our experience in treating traumatic injuries to the airway.[6] In this series, 10 patients with acute injuries and 17 with delayed traumatic laryngotracheal stenosis were evaluated and treated. All 10 of the acute injuries had excellent airway preservation; voice was preserved and successful repair of the esophagus made in one. Repair of delayed stenosis was successful in 16 of 17 patients. All but one patient had preservation of voice, despite the presence of vocal cord paralysis in 14 patients preoperatively. The cases of concomitant esophageal injury, present in four patients, were successfully repaired without development of TEF.

## Postintubation Stenosis

Postintubation tracheal injuries remain the most common indication for tracheal resection and reconstruction, despite definition of the etiology of these lesions and development

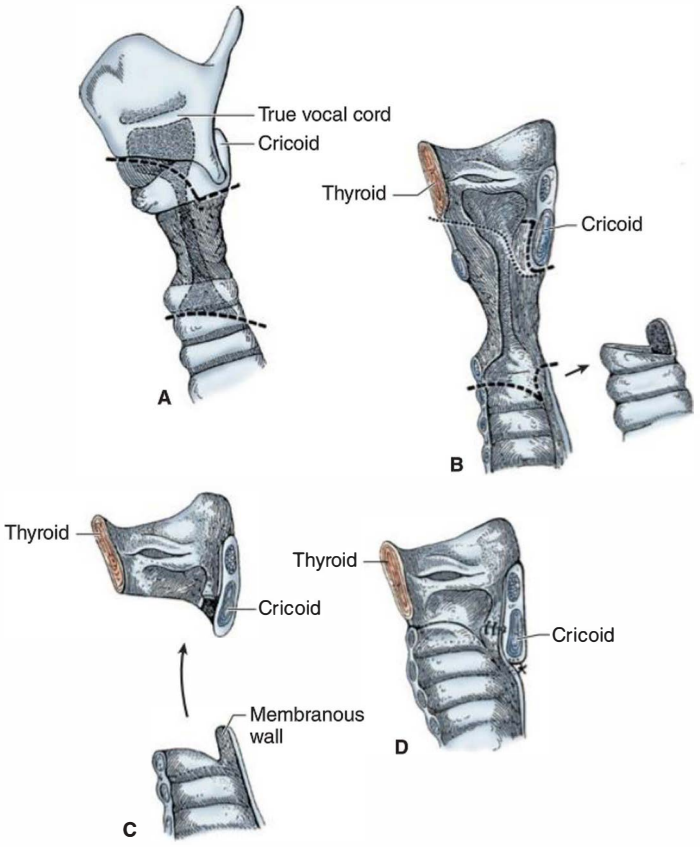



**FIGURE 8-10** Resection and reconstruction of circumferential stenosis of the subglottic larynx and upper trachea. **A.** External line of cartilaginous division of both larynx and trachea is the same as for anterolateral stenosis. **B.** Interior views of the larynx and trachea demonstrate modifications necessary when the stenosis involves the mucosa and submucosa just in front of the posterior cricoid plate. The superior dotted line indicates that the mucosa with its scarring will be cut back to within a short distance, if necessary, of the arytenoid cartilages. Inferiorly, the posterior membranous wall has been retained as a broad-based flap. **C.** Resected specimen, leaving a bare area of the intraluminal portion of the lower part of the cricoid posterior lamina. The flap of membranous wall of the trachea will be fitted into this defect to provide prompt and complete mucosal coverage. **D.** The mucosa of the larynx has been anastomosed to the mucosa of the membranous wall of the trachea. External to the lumen, connective tissue of the membranous wall has been fixed with four sutures to the inferior margin of the cricoid cartilage, ensuring that the flap will stay firmly applied to the surface. (From Grillo HC. Reconstruction after subglottic laryngeal and upper tracheal stenosis resection. *Ann Thorac Surg* 1982;33:3–18. Reprinted with permission from the Society of Thoracic Surgeons.)

of techniques for their avoidance. We reported 503 patients who underwent tracheal resection and reconstruction for postintubation lesions.[26] The balloon cuff of an endotracheal or tracheostomy tube accounted for 251 lesions; 178 lesions were at the site of a tracheostomy, and 38 patients had evidence of both lesions. In 36 patients, the exact site was uncertain, often due to prior attempts at treatment including multiple tracheostomies. Of the 503 patients, 441 had lesions that were isolated to the trachea, while 62 had concomitant involvement of the subglottic larynx.

Many patients had undergone prior attempts at surgical treatment before referral. These included resection ($n = 53$); tracheal operations such as wedge resection, splinting, or fissure ($n = 31$); and laryngeal procedures such as stenting, grafting, or fissure ($n = 20$). Sixty patients had had T tubes placed and at least 45 had had laser treatment. Eight patients had prior repairs of TEF, three of which had failed.

The initial procedure was carried out through a cervical incision in 350 patients. In 145 patients a partial upper sternal division through the sternal angle was used, with two more patients requiring the addition of right anterior thoracotomy to this approach. Six patients underwent repair via a high posterolateral thoracotomy. The amount of trachea resected ranged from 1.0 to 7.5 cm and was most commonly between 2 and 4 cm.

Of the 503 initial operations, 324 involved a trachea-to-trachea anastomosis and 117 patients had reconstructions involving partial resection of the cricoid cartilage with laryngotracheal anastomosis. In the total series of 503 patients 9.7 percent underwent laryngeal releases. However, only 8 percent of the 450 patients who had not undergone tracheal resection and reconstruction previously were deemed to need laryngeal release to reduce anastomotic tension, in comparison with 24.5 percent of the 53 who had prior resection and reconstruction. Many in the former group represent our earlier experience in tracheal surgery. Only one patient required intrapericardial hilar release.

The results have been classified as good, satisfactory, failure, and death. The result is described as good if the patient is functionally able to perform usual activities and postoperative roentgenograms or bronchoscopic examinations show an anatomically good airway. Patients are placed in the satisfactory category if they can perform normal activities but are stressed on exercise. In the absence of symptoms, this is also applied to those with abnormalities involving the vocal cords or those with significant airway narrowing evident on either endoscopic or roentgenologic examination. Failure indicates the need for a permanent tracheostomy or T tube.

The average length of follow-up was 3 years. The results were categorized as good in 440 patients and satisfactory in

31 patients; there were 20 failures and 12 deaths. Failure was treated with tracheostomy ($n = 11$), T tube ($n = 7$), or dilations ($n = 2$).

## Idiopathic Laryngotracheal Stenosis

In experienced hands, laryngotracheal resection and reconstruction is associated with excellent results and minor complications. In our experience treating this rare entity, all but 2 of 73 patients were female.[10] The duration of symptoms before evaluation varied between 4 months and 32 years, with the greatest number reporting 1 to 3 years of symptoms. At the time of referral, a total of at least 75 procedures had been performed on 28 of the 73 patients. The extent of surgical resection ranged from 1 to 5 cm with an average of 2.6 cm. Resection of the entire anterior cricoid was performed in 59 patients, while only partial or no cricoid resection was necessary in 10 and 4 patients, respectively. Thirty-six patients required mucosal resection from the posterior cricoid plate, with tracheal membranous wall advancement flap reconstruction.

Extubation in the operating room was possible in 67 of the 73 patients. These patients did not require further airway intervention during their initial hospital stay. Immediate protective tracheostomies were placed in five patients; however, only one was used in the last 30 patients of this series. One patient had a negative reexploration for postoperative cervical subcutaneous emphysema. Six patients underwent early dilation for obstructing granulation tissue.

In long-term follow-up, 66 (92 percent) patients had either excellent ($n = 19$) or good ($n = 47$) results. Of the remainder, five required only occasional dilations. A poor result was seen in one patient in whom at least yearly dilations became necessary. No patients in this series have required permanent tracheostomies or T tubes. In addition, there was no perioperative mortality.

## Tracheoesophageal Fistula

We have reported our results on the treatment of benign acquired TEFs in 38 patients.[25] The vast majority resulted from the combined effects of a nasogastric tube and either an endotracheal tube or a tracheostomy tube. The remainder were secondary to laryngotracheal trauma ($n = 5$) and complications of radiation therapy ($n = 2$) and anterior spinal fusion ($n = 2$).

Eight patients had undergone attempted repair at other institutions. Many had more than one attempted repair. The reasons for failure included the need for postoperative mechanical ventilation and failure to interpose tissue between tracheal and esophageal suture lines. Seven patients from other institutions underwent esophageal diversion with cervical esophagostomy or pharyngostomy and three had ligation or interruption of the gastroesophageal junction.

Tracheal resection and reconstruction was performed in 31 patients. This was done to address the presence of full-thickness circumferential damage at the level of the tracheal pathology or when the defect in the membranous tracheal wall was too large for direct closure. Six of these patients additionally had longitudinal closure of the membranous wall of the trachea where the fistula had been located. The amount of injured trachea would have been too excessive to allow reconstruction otherwise. Five patients had laryngotracheal resection because of pathology involving the subglottic larynx. Tracheal damage was too extensive in one patient to allow tracheal resection; therefore a T tube was placed following repair of the fistula. There has been no recurrence of the fistula in this patient and a good airway is maintained in this fashion.

Thirty-three patients had direct closure of the esophageal fistula by using a two-layer closure as described. Some narrowing of the esophageal lumen is inevitable in this situation but is well tolerated by most patients. Because of prior cervical esophagostomy, five patients underwent end-to-end esophageal anastomosis. Thirty-four patients had interposition of a local strap muscle between the esophageal and tracheal suture lines. Cervicomediastinal exenteration with creation of a mediastinal tracheostomy and a substernal colon bypass was required for a TEF following laryngectomy and irradiation.

Four patients died following the repair of TEFs (10.5 percent). Three of these died following attempted transthoracic repair of very distal TEF. All had extensive mediastinal sepsis at the time of repair and required mechanical ventilation after surgery. The fourth death occurred in a young man who underwent extensive tracheal resection with laryngeal release. Tracheal separation occurred on the sixth postoperative day and the patient could not be resuscitated.

Two patients developed small recurrent TEFs requiring reoperation. Both had previous cervical esophagostomies and required end-to-end anastomoses. Theses recurrent fistulas were small and were successfully managed by short tracheal resection and closure of the esophageal defect. Tracheal stenosis developed at the level of the retained stoma in one patient and was corrected by a second tracheal resection.

Of the 34 surviving patients, 33 were able to take aliment orally. Five patients required esophageal dilatation for narrowing at the level of the repair of the esophageal fistula. None still require dilation. The one patient who does not take aliment orally is also one of two patients requiring a tracheal appliance to provide an airway. Another patient requires a T tube because of the extent of injury to her airway.

Single-stage repair of a TEF gives excellent results, with a low incidence of recurrent fistulas. These results continue to support the approach outlined for management of acquired nonmalignant TEFs.

## Primary Tracheal Tumors

Gaissert summarized the 40-year cumulative experience at Massachusetts General Hospital of treating primary ACCs and SCCs of the trachea.[13] During this time, 270 patients

**TABLE 8-1: Experience with Primary Tracheal Carcinoma Over Four Decades a t Massachusetts General Hospital[a]**

| Decade | Total Patients (*N*) | ACC Patients (*N*) | SCC Patients (*N*) | Resections Performed (*N*) | Resection Rate (%) | Hospital Mortality (%) |
|---|---|---|---|---|---|---|
| 1962–1971 | 19 | 7 | 12 | 13 | 68 | 21 |
| 1972–1981 | 54 | 29 | 25 | 33 | 61 | 11 |
| 1982–1991 | 107 | 54 | 53 | 71 | 66 | 5 |
| 1992–2001 | 88 | 43 | 45 | 72 | 82 | 3 |
| Total | 268 | 133 | 135 | 189 | 71 | 7 |

ACC, adenoid cystic carcinoma; SCC, squamous cystic carcinoma.

[a]Two patients operated on in 2002 were excluded from the table.

were evaluated, with histologic distribution equally distributed between ACC and SCC. Resection was performed in 191 (71 percent) patients, with an operative mortality of 7.3 percent (14 of 191). Importantly, both rates of resection and hospital mortality have improved with e ach decade (Table 8-1). As our experience has grown, operative mortality has decreased from 21 percent in the 1960s to 3 percent in this last decade.

Resection was not performed in 79 patients, 34 in those with ACC (25 percent) and 45 patients with SCC (33 percent). Contraindications to resection have included tumor length (67 percent) and locoregional extent (24 percent) in the vast majority of cases, with distant metastases only rarely present (7 percent). The determination of unresectability was made during operative exploration in 17 of 208 patients (8 percent). ACCs tended to be longer lesions and were also associated with more significant locoregional extension. This explains the more frequent observation of ACC resection with positive microscopic tracheal and radial margins (59 percent) as compared with SCCs (18 percent).

The overall survival for all patients with primary tracheal carcinoma was 84 percent at 1 year, 45 percent at 5 years, and 25 percent at 10 years. Mean survival was 38 months in resected SCCs, 8.8 months in resectable SCCs, 69 months in resected ACCs, and 41 months in unresectable ACCs. Notably, survival after incomplete resection of ACCs was still 14.5 percent at 15 years.[16] Multivariate analysis identified ACCs and complete resection to be associated with 5-year survival and ACCs, complete resection, and age to be associated with 10-year survival. Tumor length, lymph node status, or type of resection did not influence long-term survival.[28]

The presence of tumor at the resection margins of ACCs, even by frozen section during operation, has particular importance in airway reconstruction. The surgeon must often compromise complete resection for the sake of safety, and the above data indicate that a small though not statistically significant survival benefit exists in these patients. All these patients now receive postoperative irradiation. Suture line recurrence thus far has been rare, and late recurrence has been that of distant disease. In contrast, irradiation of unresected tumor is all but uniformly characterized by local recurrence in 3 to 5 years despite a good response early.

We separately analyzed clinical and pathologic characteristics of resected squamous cell tumors to determine prognostic factors. All five patients with tumor extension into the thyroid gland died of disease within 3 years. Lymphatic invasion and poorly differentiated tumors were associated with worse prognosis, while keratinization, necrosis, and tumor thickness were not.[29]

The analysis of this 40-year experience with surgical management of primary tumors of the trachea appears to confirm and extend conclusions based on previously reported experiences.[30] Primary ACCs and SCCs of the trachea are best treated by resection when primary reconstruction may be safely accomplished. Resection should be followed by full-dose mediastinal irradiation in most cases.

## COMPLICATIONS

Complications following tracheal surgery are similar regardless of the problem for which resection and reconstruction is performed. Wright and colleagues[31] recently presented the most complete analysis of anastomotic complications after tracheal resection. This review of 901 patients identifies relevant risk factors for the development of these problems and further describes their management. Anastomotic complications include granulations at the suture line, stenosis, and tracheal separation.

A significant reduction in suture granuloma formation has been seen since the conversion to absorbable suture material used for the anastomosis. In fact, the use of absorbable Vicryl sutures since 1978 has all but eliminated suture-related granulations. These can be successfully managed with bronchoscopic suture removal and local steroid injection. More extensive processes may require reoperation for resection, T-tube placement, or tracheostomy.

Stenosis and separation of a tracheal, carinal, or bronchial anastomosis are feared complications of airway reconstructive surgery. Excessive tension on an anastomosis is probably the most frequent cause of technical failures.

Dangerous tensions may appear after resection of more than 50 percent of the trachea in the adult and of more than 30 to 40 percent in the child. These are very general percentages and do not apply to specific individuals, who may vary widely with respect to age, body habitus, pathology, prior surgery, and other comorbidities. Carinal resections are particularly at risk because of the complex nature of the reconstructions required and the fact that primary tumors may involve a considerable length of trachea as well as of main bronchi.

Several predictors of anastomotic complications were demonstrated: reoperation, diabetes, lengthy (≥4 cm) resections, laryngotracheal resections, age ≤17 years, and need for a tracheostomy before operation. The frequency of anastomotic complications was higher in patients undergoing operations for TEF than in those being treated for tracheal tumors, postintubation stenoses, and idiopathic laryngotracheal stenoses. Of note, corticosteroid use was not associated with an increase in complication rate. This is most likely secondary to the management strategy of our group, which is to defer tracheal operations in the presence of high-dose steroids until such drugs can be effectively tapered.

Overall, 81 patients experienced anastomotic complications in this series. Thirty-seven patients had separation of the suture line, another 37 patients developed anastomotic stenosis, and 7 had airway obstruction from granulation tissue formation.

Complications were treated with multiple dilations ($n = 2$), temporary tracheostomy ($n = 7$) or T-tube ($n = 16$) placement, permanent tracheostomy ($n = 14$) or T-tube ($n = 20$) placement, and reoperation ($n = 16$). The mortality of patients who had anastomotic complications was 7.4 percent (6 of 81), compared with 0.06 percent (5 of 820) in those without anastomotic complications. In this series, no patient has died due to their anastomotic complications since 1988. This success is attributed to the routine use of postoperative bronchoscopy and the early recognition and subsequent definitive management of anastomotic complications.

With attention to detail, even complications can be successfully managed. Successful management not only saves a life but also preserves the airway and voice.

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## TRACHEAL DISEASES BOARD REVIEW QUESTIONS (CHAPTER 8)

1. Predictors of anastomotic complications after tracheal resection include all of the following except?
   A. Diabetes
   B. Reoperative tracheal surgery
   C. Female gender
   D. Length of resection
   E. Age less than 18 years

2. A 45-year old woman is undergoing tracheal resection for adenoid cystic carcinoma. A 4-cm tracheal resection is performed through a cervical incision, with the distal extent of resection located 4 cm from the carina. The tumor has been grossly resected, but there are malignant cells at the distal margin. Which of the following is the correct next course of action?
   A. Partial sternotomy, laryngeal release, and resection of additional trachea with primary reconstruction, postoperative radiotherapy.
   B. Right thoracotomy, pericardial release, and resection of additional trachea with primary reconstruction.
   C. Right thoracotomy, resection of additional trachea with mediastinal tracheotomy.
   D. Tracheal reconstruction, postoperative chemotherapy.
   E. Tracheal reconstruction only.

3. A 74-year-old man develops a tracheoesophageal fistula due to prolonged ventilator support and tracheostomy. Which of the following is the most appropriate treatment?
   A. Tracheal and esophageal covered stent deployment.
   B. Immediate repair of fistula with muscle interposition.
   C. Replacement of tracheostomy appliance with balloon below fistula and decompressive gastrotomy and jejunostomy until no longer requiring mechanical ventilation.
   D. Treatment with antibiotics and tube feeding until no longer requiring mechanical ventilation.
   E. Esophageal exclusion.

4. A patient with known postintubation stenosis presents to the ER with progressive dyspnea after an upper respiratory infection. Although well saturated with face mask oxygen, she cannot speak in full sentences and is anxious. Which of the following is the most appropriate initial treatment?
   A. Rigid bronchoscopy with tracheal dilation in the operating room.
   B. Flexible bronchoscopy in the emergency department.
   C. Immediate fiberoptic intubation.
   D. Tracheostomy in the operating room.
   E. Intravenous steroids and nebulized epinephrine.

5. Which of the following does not decrease tension during tracheal resection?
   A. Neck flexion
   B. Mobilization of the pretracheal plane
   C. Circumferential tracheal dissection
   D. Suprahyoid laryngeal release
   E. Pericardial hilar release

## ANSWERS

1. **Answer: C.** Female gender is not a predictor of anastomotic complication after tracheal resection.
2. **Answer: A.** Partial upper sternotomy, with or without laryngeal release, will allow for additional tracheal resection from a cervical approach.
3. **Answer: B.** Single-stage repair provides a definitive treatment with excellent results. Muscle or omental interposition is the key to reducing the incidence of fistula recurrence in patients on mechanical ventilation.
4. **Answer: A.** Patients with airway strictures are best managed in the controlled setting of the operating room with rigid bronchoscopy and dilation. Tracheostomy should be avoided, as this can result in more extensive stricture formation of a longer segment of trachea.
5. **Answer: C.** Circumferential tracheal dissection has little effect on mobilization and can result in devascularization of the trachea with associated suture line breakdown.

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# 9 Primary Lung Cancer

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**KEY CONCEPTS**

- Epidemiology
  - Lung cancer is a leading cause of preventable death attributed to smoking and environmental exposure. Its highest incidence is in men but recent trends have shown a significant increase in women paralleling the trend of smoking prevalence in different genders.
- Pathophysiology
  - Most of lung cancer is the result of a series of genetic changes caused by environmental factors that allow cells to grow, proliferate, and metastasize.
- Clinical features
  - Most lung cancer patients present with late-stage disease. Patients' clinical symptoms depend on the location and size of the tumor and the presence of metastasis.
- Diagnostics
  - Lung cancer diagnosis is accomplished through the pathologic examination of a biopsied specimen of the mass. Clinical staging is based on a combination of patient history, physical exam, and radiographic information along with pathologic examination of the primary tumor, mediastinal lymph nodes, and any suspected sites of metastasis.
- Treatment
  - Lung cancer patients are treated with surgery, radiotherapy, and/or chemotherapy. Surgery and radiotherapy are used for local and regional lung cancer; surgery is the primary therapy, and radiotherapy is used in patients who cannot tolerate surgery. Chemotherapy is used to treat patients with regional or metastatic lung cancer.
- Prognosis
  - Overall, the prognosis for lung cancer is poor. The estimated overall 5-year survival rate for all of the patients with lung cancer is about 16 percent; however, patients with resected pathologic early-stage lung cancer can achieve a 5-year survival rate of 70 to 80 percent. The type and pathologic stage of lung cancer is the best predictor for prognosis.

## INTRODUCTION

### Historical Highlights

Lung cancer, once considered rare at the beginning of the 20th century, became a frequently diagnosed disease by the mid-1930s. Oschner and Debakey attributed the increased incidence to the rise in smoking, a link that was later supported by the findings of a case-control study in 1939.[1] The surgical treatment of lung cancer has evolved over time. The first successful single-stage pneumonectomy was performed by Graham and Singer in 1933,[2] and the modern technique of ligating individual pulmonary vessels and suturing the bronchus was first described by Reinhoff in 1947.[3]

## PATHOLOGY

Lung cancer originates from epithelial cells. The two broad categories of lung cancer are nonsmall cell lung cancer (NSCLC), which constitutes about 80 percent of lung cancers, and small cell lung cancer (SCLC).

### Nonsmall Cell Lung Cancer

#### ADENOCARCINOMA

Adenocarcinoma, the most common type of NSCLC, is a malignant epithelial tumor with glandular differentiation or mucin production. Adenocarcinomas are white, fleshy

solid tumors that are usually located in the periphery of the lung and involve the pleura and chest wall in 15 percent of patients. There are five macroscopic growth patterns of adenocarcinoma; the most common pattern is peripheral tumor with desmoplastic fibrosis retracting the overlying pleura. Other patterns include central or endobronchial adenocarcinoma, diffuse pneumonia-like consolidation or papillary growth, diffuse pleural thickening or pseudomesotheliomatous carcinoma, and adenocarcinoma arising in the background of underlying fibrosis. There are four distinct histologic patterns or subtypes of adenocarcinoma. They are acinar, papillary, bronchioloalveolar, and solid adenocarcinoma with mucin production. It is uncommon to have an adenocarcinoma consisting entirely of one histologic pattern. Most tumors have mixed histology although one subtype is frequently dominant. Immunohistochemistry of adenocarcinoma reveals the expression of the epithelial markers cytokeratin 7 (CK7) and thyroid transcription factor-1 (TTF-1).[4] As the name implies, TTF-1 is a protein that not only regulates transcription of genes specific for thyroid, but is also specific for lung. Patients with lung tumor that is positive for TTF-1 but negative for thyroglobulin, a protein produced exclusively by thyroid, confirm that the tumor arises from the lung.

#### SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma, which constitutes approximately 40 percent of NSCLC, is a malignant, typically cavitary tumor that arises centrally from bronchial epithelium. Squamous cell carcinomas are usually white or gray and grow laterally along the bronchial mucosa ("creeping type") or downward ("penetrating type"). Squamous cell carcinomas tumors show keratinization, pearl formation, and/or intercellular bridges on histopathologic examination, and immunohistochemistry reveals keratin, carcinoembryonic antigen, and cytokeratin 5 and 6 expression.[4]

#### LARGE CELL CARCINOMA

Large cell carcinoma, which constitutes about 9 percent of NSCLC, is a poorly differentiated epithelial tumor consisting of sheets or nests of large polygonal cells with vesicular nuclei and prominent nucleoli. Large cell carcinoma is usually diagnosed by excluding other tumor types during histopathologic examination. Most large cell carcinomas are located in the peripheral lung and invade the visceral pleura, chest wall, or adjacent structures.

#### NEUROENDOCRINE TUMORS

Neuroendocrine tumors range from indolent to aggressive. The four types of neuroendocrine tumors—typical carcinoid, atypical carcinoid, small cell lung cancer, and large cell neuroendocrine carcinoma—all exhibit organoid nesting, palisading, a trabecular pattern, and a rosette-like structure. The main criterion used to distinguish the different types of neuroendocrine tumor is the number of mitoses per 10 high-power fields of magnification. Typical carcinoid tumors have two mitoses or less and do not have necrosis, atypical carcinoid tumors have between 2 and 10 mitoses or evidence of necrosis, and small cell lung cancers and large cell neuroendocrine carcinomas have 11 or more. A constellation of features distinguishes small cell lung cancer and large cell neuroendocrine carcinoma. Large cell neuroendocrine carcinoma has cytologic features of NSCLC with large cell size, low nuclear-to-cytoplasmic ratio, vesicular chromatin, and frequent nucleoli. On the other hand, small cell carcinoma has scant cytoplasm and absent or faint nucleoli. Immunohistochemistry of neuroendocrine tumors reveals cytokeratin, chromogranin, synaptophysin, CD57, and CD56 expression.[4]

#### OTHER TUMORS

Adenosquamous carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, epithelial–myoepithelial carcinoma, and sarcomatoid carcinoma compose about 2 percent of NSCLC.[5]

### Small Cell Lung Cancer

Small cell lung cancer is an epithelial tumor that consists of small cells with scant cytoplasm, ill-defined borders, finely granular nuclear chromatin, and absent nucleoli. Small cell lung cancer is usually a hilar or perihilar mass with mediastinal lymphadenopathy. The tumors are typically white-tan, soft, friable masses with extensive necrosis. Immunohistochemistry of small cell lung cancer reveals TTF-1, CD56, chromogranin, and synaptophysin expression.

## PATHOPHYSIOLOGY

Development of lung cancer is considered as a series of genetic changes induced by environmental factors, which leads a normal cell to develop into a cancer. These genetic changes are mutations of the tumor oncogenes and tumor suppressors as well as the change in the tumor microenvironment that allows the tumor to grow and metastasize into other organs.

### Oncogenes and Tumor Suppressors

The two most common types of NSCLC are adenocarcinoma and squamous cell carcinoma, both of which develop from normal epithelium into invasive cancer through a series of genetic mutations of tumor oncogenes and tumor suppressors. In adenocarcinoma, the first histologically noticeable change is the development of atypical adenomatous alveolar hyperplasia, which then develops into bronchoalveolar carcinoma and ultimately invasive adenocarcinoma. The genetic changes that have been associated

with this progression include mutations of the Kirsten rat sarcoma (K-RAS) viral oncogene homolog and epithelial growth factor receptor (EGFR) oncogenes as well as the p53 and p16 tumor suppressor genes. K-RAS encodes a membrane-associated G protein that serves as a link between tyrosine kinase receptors at the membrane and cytoplasmic second messenger molecules. Mutated K-RAS, which is found in 10 to 30 percent of lung adenocarcinomas, constitutively activates guanosine triphosphatase, which causes tumor cells to proliferate.[6] About 10 to 40 percent of adenocarcinomas with wild-type K-RAS have an EGFR mutation, which has been associated with women, nonsmokers, and patients with bronchoalveolar adenocarcinomas.[6] Mutated EGFR binds such ligands as EGF or transforming growth factor alpha and activates tyrosine kinase-containing signaling pathways, leading to tumor cell proliferation.[7,8]

The p53 and p16 tumor suppressor genes are also involved in adenocarcinoma development. The p53 encodes a transcription factor that mediates cell cycle arrest and cell death after DNA damage.[9] When p53 is mutated, cell division is uninhibited, and cell death is not induced, thus allowing tumor cells to proliferate. In contrast to p53's mechanism of action, the p16 tumor suppressor gene activates the retinoblastoma (Rb) gene to cause cell cycle arrest at the $G_1$/S boundary. The most common p16 mutation is a loss of heterozygosity that is found in about 50 percent of lung adenocarcinomas and allows tumor cells to proliferate without inhibition.

Similar multistage changes lead to invasive squamous cell carcinoma of the lung. The transition from normal epithelium to squamous hyperplasia is the first detectable histologic change of the squamous cell epithelium. The cells then develop into squamous metaplasia, dysplasia, carcinoma in situ, and ultimately invasive carcinoma. Oncogene and tumor suppressor mutations occur at each stage of development. As in adenocarcinoma, p53 mutations are common in squamous cell carcinoma with a mutation rate of 60 to 70 percent[6]; however, very few K-RAS mutations (<1%) and EGFR mutations (<1%) occur in squamous cell carcinoma.[6]

About 90 percent of small cell lung carcinomas have p53 and/or Rb mutations. The Rb gene, which is downstream of the p16 pathway, impacts cell cycle regulation, and mutation of Rb leads to tumor cell proliferation. The Myc oncogene, a nuclear phosphoprotein that regulates cell growth and tumorigenesis, is amplified in 30 percent of small cell lung carcinomas.[4]

### Tumor Microenvironment

Invasive carcinomas alter their environment to enable their growth, survival, and metastasis by releasing certain factors such as vascular endothelial growth factor (VEGF), which signals for angiogenesis.[10] Invasive carcinomas also recruit leukocytes such as T cells and macrophages to enable metastasis. It is a complex interplay between the tumor and the environment, which allows the cancer to grow and escape its primary site of origin.

## CLINICAL FEATURES

### Epidemiology

In 2009, nearly 220,000 people were diagnosed with lung cancer in the United States and over 159,000 people died of the disease.[11] The overall 5-year survival for all lung cancer patients is 16 percent. Survival depends heavily on the stage of the disease at diagnosis. The lifetime risk for developing lung cancer in the United States is 1 in 14.[11] In the United States, the population-attributable risk of developing lung cancer is 90 percent from smoking, 10 percent from radon, 9 to 15 percent from other occupational exposures, 1 to 2 percent from outdoor pollutants, and <1 percent from dietary factors.

Lung cancer is one of the leading causes of preventable death. Smoking has long been known to cause lung cancer. The number of years and the volume of cigarettes (packs per day) that a person smokes are directly related to the risk of that person developing lung cancer. Active cigarette smokers are 20 times as likely as nonsmokers to develop lung cancer. Quitting smoking reduces a smoker's risk of developing lung cancer; however, this reduced risk never equalizes to that of a never-smoker. In never-smoker, 25 percent of lung cancers are due to secondhand smoke. Studies have shown that people regularly exposed to secondhand smoke have a 30 percent higher risk of developing lung cancer than people who have never been or are rarely exposed to secondhand smoke.[12]

The second leading cause of lung cancer is radon, the first occupational carcinogen associated with lung cancer. Other occupational hazards include arsenic, chromates, chloromethyl ethers, nickel, polycyclic aromatic hydrocarbons, and asbestos. Both smoking and asbestos exposure are independent risk factors for lung cancer; combined, they act synergistically to further increase the risk of developing lung cancer.[12]

The pattern of lung cancer incidence in the United States over the years reflects cigarette use among men and women. The rapid rise in smoking prevalence first occurred in men and then a parallel rise was seen in women 30 years later. This same pattern has also been seen in lung cancer prevalence. The lung cancer incidence among men, although still much higher than that among women, has peaked and begun to decline; however, lung cancer incidences in women continue to rise.

Racial differences have also been identified. Currently, African American men are at the highest risk for lung cancer. Although African American women and white women have the same risk for developing lung cancer, African American men have a significantly higher risk than white men for unknown reasons. Latinos, Native Americans, and Asians/Pacific Islanders have a significantly lower risk of lung cancer than whites and African Americans. A family history of lung cancer also increases one's risk of developing the disease. Some researchers have postulated that consuming fruits and vegetables has a protective effect against lung cancer.[12]

## Screening

A randomized control trial performed by The National Lung Screening Trial Research Team showed that patients who had low-dose CT performed yearly for 3 years showed a 20% relative reduction in mortality from lung cancer compared with patients who underwent three annual screenings of chest radiography. The group enrolled 53,454 patients who were at high risk for developing lung cancer and followed them for 5 years. The study showed that patients who were between 55 and 74 years of age with at least 30 pack-years history of smoking, or if former smoker, quit within the previous 15 years, had benefits from CT screening.[13] This study provides definitive data on the role of CT screening for lung cancer and it should be recommended for patients who are at high risk for developing lung cancer.

## Clinical Presentation

Lung cancer patients are typically in the fifth to seventh decades of life. Patients with early-stage lung cancer have clinically silent tumors and they are a minority. Most patients present with symptoms due to advanced disease.

### PULMONARY SYMPTOMS

Cough is the most common presenting pulmonary symptom in lung cancer patients. Other pulmonary symptoms include dyspnea, hemoptysis, and sputum production. Tumors obstructing the airway may cause atelectasis, obstructive pneumonitis, and/or pneumonia. Tumor invasion into the bronchial artery or other major blood vessels can cause hemoptysis. Pleural effusion caused by the tumor may result in dyspnea.[14]

### NONPULMONARY SYMPTOMS

Like many other cancer patients, lung cancer patients sometimes present with weight loss, fatigue, malaise, and anorexia. Patients can also present with symptoms caused by the tumor invading adjacent structures. Focal chest pain suggests chest wall or spinal involvement from local invasion or bone pain stemming from metastatic disease. Direct invasion or nodal involvement may lead to superior vena cava syndrome or invasion of the recurrent laryngeal nerve resulting in hoarseness. Involvement of the superior cervical ganglion can cause Horner syndrome, which is characterized by unilateral facial anhidrosis, ptosis, and miosis. Shoulder and arm pain may occur if an apical tumor invades the brachial plexus.

Although lung cancers can metastasize to every part of the body, they most commonly metastasize to the brain and bones, causing a number of distinct symptoms. Lung cancer metastasis in the bone can cause bone pain and/or pathologic fractures. Metastatic lesion in the brain is seen in about 10 percent of patients with lung cancer and it can cause neurologic changes. Additional common sites of metastasis include residual lung, the liver, and the adrenal glands.

About 10 percent of NSCLC patients present with paraneoplastic syndrome. The most common sign associated with the paraneoplastic syndrome is clubbing. In addition, patients may manifest endocrine symptoms such as hypercalcemia, Cushing syndrome, syndrome of inappropriate antidiuretic hormone hypersecretion, carcinoid syndrome, hypercalcitoninemia, hyperglycemia, and hyperthyroidism.

# DIAGNOSIS AND STAGING (SEE ALSO CHAPTER 3)

## Diagnostic Studies

Chest radiographs showing lung nodules should be compared with previous imaging studies to determine whether the nodule is new or has grown. Patients with new or growing nodules and patients for whom previous imaging studies are unavailable should undergo chest CT to determine whether the nodule has features indicative of malignancy. Features such as a noncalcified spiculated lesion are very concerning for malignancy. There are predictive scoring systems based on both radiologic and clinical features.[15] If malignancy is suspected, diagnostic CT-guided fine-needle aspiration biopsy of the nodule should be performed. Endobronchial ultrasonography or magnetic navigation system can be used to guide fine-needle aspiration biopsy if CT guidance is not possible. If image-guided fine-needle aspiration biopsy is not possible or if the risk of malignancy, based on clinical and radiographic features, is very high then video-assisted thoracoscopic surgery (VATS) or open thoracotomy and biopsy can be done to obtain a definitive diagnosis.

## Staging

The clinical staging is performed using different tests to obtain the most accurate tumor–node–metastasis (TNM) staging of the patient. The T or tumor size and extent can be determined best by the CT scan of the chest. Next, the M and N stages are determined using a positron emission tomography (PET)/CT to identify metastatic disease and determine mediastinal lymph node involvement. If patient has a high-stage tumor based on PET/CT or if the patient has any neurologic symptoms, magnetic resonance imaging of the brain is performed to evaluate the brain for evidence of metastatic disease. A PET/CT used for lung cancer staging is not ideally suited to detect metastatic lesions to the brain. If there are positive lymph nodes in the mediastinum based on the PET/CT or the patient has a very large or central primary tumor then endobronchial ultrasonography with transbronchial biopsy or mediastinoscopy is used to evaluate the mediastinum for metastatic disease.

### SMALL CELL LUNG CANCER

Small cell lung cancer has classically been staged as either limited or extensive disease. The limited disease is restricted to one hemithorax and may be accompanied by ipsilateral pleural effusion and/or regional metastases in the ipsilateral and contralateral hilar, mediastinal, or supraclavicular lymph nodes. All other small cell lung cancers are defined as extensive disease. The recent edition of the staging system does advocate that TNM staging should also be used in staging small cell lung cancer.

### NONSMALL CELL LUNG CANCER

The guidelines for the 7th edition of the NSCLC staging system were set forth by the International Association for the Study of Lung Cancer (IASLC).[16] This TNM system (Table 9-1) provides information about the extent of the primary tumor, extent of metastatic disease in regional lymph nodes (Fig. 9-1), and absence or presence of distant metastasis. The system can be applied to both clinical (cTNM) and postresection histopathologic (pTNM) assessments of NSCLC.[16]

Stages IA and IB describe small tumors that have not metastasized to the lymph nodes or other organs. Stage IA disease includes T1a tumors <2 cm and T1b tumors 2 to 3 cm (Fig. 9-2). Stage IB disease includes T2a tumors 3 to 5 cm (Fig. 9-3). Stages IIA and IIB describe larger tumors without lymph node involvement and small tumors with ipsilateral hilar lymph node involvement. Stage IIA disease includes T1a, T1b, and T2a tumors with N1, ipsilateral hilar lymph node involvement (Fig. 9-4) as well as T2b tumors 5 to 7 cm. Stage IIB disease includes T2b tumors with N1 involvement and T3 tumors. T3 is defined by size (>7 cm) but also includes tumors that invade resectable structures (the chest wall, diaphragm, phrenic nerve, mediastinal pleura, and parietal pericardium) endobronchial tumors that are <2 cm from carina (but not involving the carina), obstructing tumors that cause atelectasis or pneumonitis of an entire lung, and satellite tumors in the same lobe (Fig. 9-5).

Stage IIIA describes a set of tumors that involve the ipsilateral mediastinal lymph nodes (N2 disease; Fig. 9-6), advanced tumors with hilar lymph node involvement, or T4 tumors. They are T1, T2, or T3 tumors with N2, ipsilateral mediastinal lymph node involvement, T3 or T4 tumors with N1 involvement. T4 describes very advanced tumors that invade structures that are difficult to resect (heart, great vessels, recurrent laryngeal nerve, esophagus, vertebral body, and carina) or that possess a satellite tumor in a different lobe but within the ipsilateral lung (Fig. 9-7).

Stage IIIB describes T4 tumors with N2 disease or any tumor with N3, contralateral mediastinal lymph node disease (Fig. 9-8). Finally, stage IV describes any tumor with metastatic disease to other organs including the contralateral lung or malignant effusions (pleural or pericardial) (Figs. 9-9 and 9-10).

**TABLE 9-1: Summary of TNM Characteristics**

| | |
|---|---|
| TX | Positive Cytology Only |
| T1 | ≤3 cm |
| T1a | ≤2 cm |
| T1b | >2–3 cm |
| T2 | Main bronchus ≥2 cm from carina, invades visceral pleura, partial atelectasis |
| T2a | >3–5 cm |
| T2b | >5 cm–7 cm |
| T3 | >7 cm; chest wall, diaphragm, pericardium, mediastinal pleura, main bronchus <2 cm from carina, total atelectasis, separate nodule(s) in same lobe |
| T4 | Mediastinum, heart, great vessels, carina, trachea, oesophagus, vertebra, separate tumor nodule(s) in a different ipsilateral lobe |
| N1 | Ipsilateral peribronchial, ipsilateral hilar |
| N2 | Subcardial, ipsilateral mediastinal |
| N3 | Contralateral mediastinal or hilar, scalene or supraclavicular |
| M1 | Distant metastasis |
| M1a | Separate tumor nodule(s) in a contra-lateral lobe; pleural nodules or malignant pleural or pericardial effusion |
| M1b | Distant metastasis |

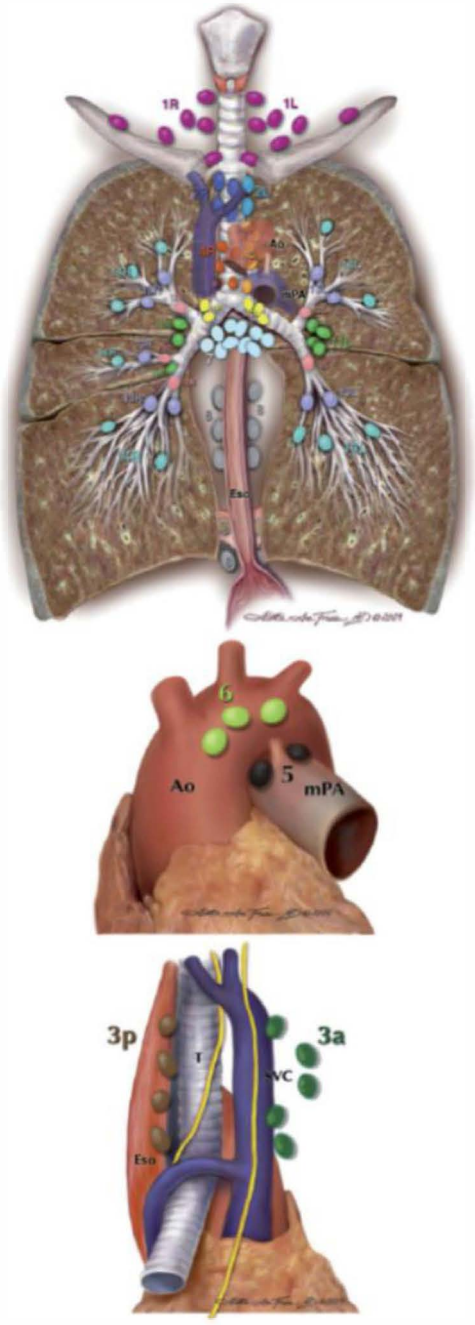
Data from *TNM Classification of Malignant Tumours*, 7th Edition, L.H. Sobin and Ch. Wittekind (eds). Copyright 2009 Wiley, New York.

## Future of Staging

Despite the improvements in prognostication with the revised staging system, patients in each stage remain heterogeneous with respect to their individual outcome. For example, 20 to 30 percent of T1aN0M0 tumor still recurs despite their early stage. Clearly this is due to the inherent biology of the tumor, which is not reflected in an anatomical staging system. Kratz et al. have shown that the 14 gene signature can be used to determine prognosis in patients with small node-negative lung tumors.[17] The study shows that the 14 gene signatures can show which subgroup of patients may have worse prognosis. This may eventually lead to the addition of "biologic" or B category to our TNM classification system in the future.

## MULTIMODALITY THERAPY

There are three modalities to treat lung cancer: surgery, radiotherapy, and chemotherapy. Conceptually radiotherapy and surgery are therapies directed at local and regional disease whereas chemotherapy can address regional and metastatic disease. For curative intent, surgery does provide better overall survival compared with radiation for local disease. Radiotherapy is still a curative option especially for patients who cannot tolerate lung resection secondary to reduced lung function or significant comorbidities. Radiotherapy can also be used for palliation of




*Supraclavicular zone*
1 Low cervical, supraclavicular, and sternal notch nodes

**SUPERIOR MEDIASTINAL NODES**

*Upper zone*
2R Upper Paratracheal (right)
2L Upper Paratracheal (left)
3a Prevascular
3p Retrotracheal
4R Lower Paratracheal (right)
4L Lower Paratracheal (left)

**AORTIC NODES**

*AP zone*
5 Subaortic
6 Para-aortic (ascending aorta or phrenic)

**INFERIOR MEDIASTINAL NODES**

*Subcarinal zone*
7 Subcarinal

*Lower zone*
8 Paraesophageal (below carina)
9 Pulmonary ligament

**N1 NODES**

*Hilar/Interlobar zone*
10 Hilar
11 Interlobar

*Peripheral zone*
12 Lobar
13 Segmental
14 Subsegmental

**FIGURE 9-1** International Association for the Study of Lung Cancer Nodal Chart with Stations and Zones. (Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2008 Aletta Ann Frazier, MD.)

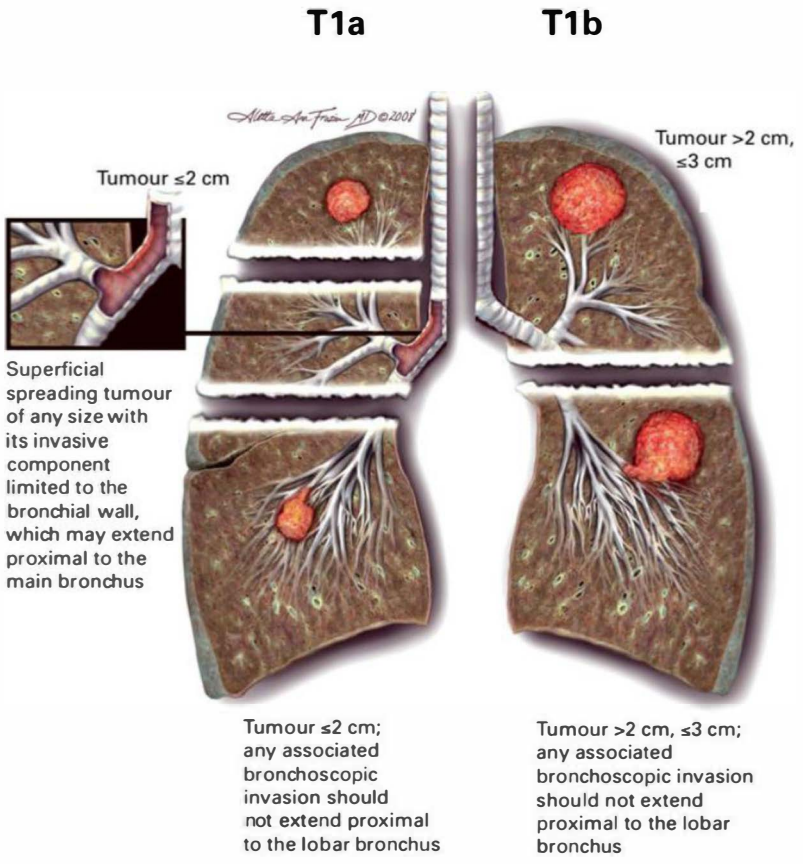



**FIGURE 9-2** Representation of T1a and T1b lung cancer. (Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2008 Aletta Ann Frazier, MD.)

symptomatic metastatic disease especially the brain and the bone. Below are some general guidelines for specific clinical stages.

## Stage I and II Nonsmall Cell Lung Cancer

Surgery is the recommended initial treatment for patients with stage I or II lung cancer (Table 9-2). If pathology reveals positive margins following lung cancer resection, and the patient cannot tolerate additional pulmonary resection, radiotherapy can be offered to reduce the rate of local recurrence. Radiotherapy is also advocated in patients with early-stage disease who cannot tolerate lung resection because of poor medical condition or poor pulmonary function. Adjuvant chemotherapy should be considered for patients with pathologic stage II lung cancer as it has been shown to improve disease-free survival.

### SURGERY

The main goals of lung cancer surgery in patients with stage I or II disease are to completely remove the tumor, all associated hilar and intrapulmonary lymph nodes, and at least sample the ipsilateral mediastinal lymph nodes. If the tumor is locally invasive to nearby structures, en bloc resection should be performed and the margins sampled using frozen section biopsy to ensure that all of the tumor is resected. Similarly, frozen section evaluation of the bronchial margin should be performed. If either margin is positive, then the appropriate resection should be performed until a negative margin is obtained. If a positive margin remains and the patient cannot tolerate a further resection, postoperative radiotherapy to the involved margin is warranted.

Two surgical issues must be addressed when treating patients with stage I or II lung cancer. The first issue concerns the volume of lung that should be removed with the tumor (lobectomy or sublobar resection). The Lung Cancer Study Group randomized stage I tumors to lobectomy versus a sublobar resection. Lobectomy provided significantly longer disease-free survival and a lower recurrence rate than sublobar resection. However, the survival advantage was unable to achieve a statistically significant difference. On the basis of these findings, lobectomy remains the standard surgical treatment for NSCLC.[18] Improvements in imaging have allowed tumors to be identified at an

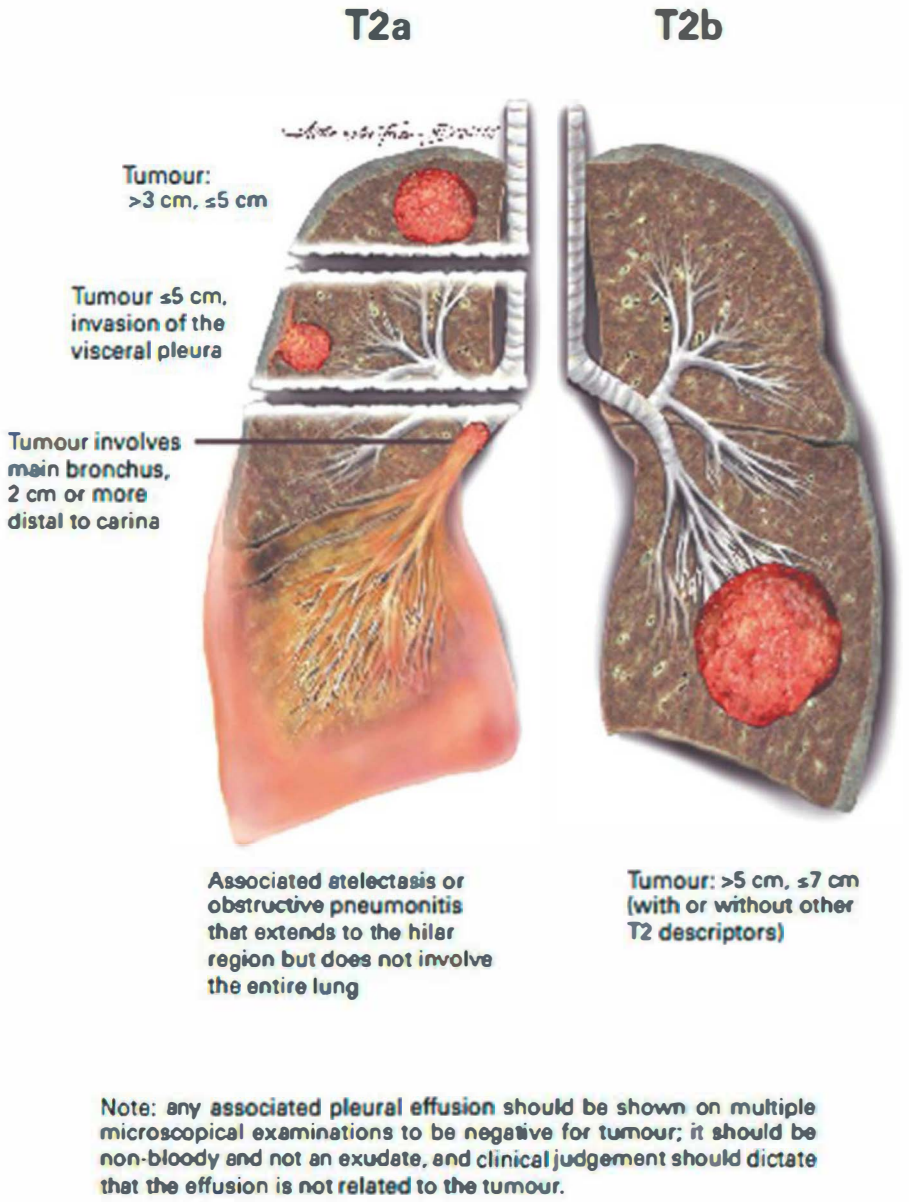



**FIGURE 9-3** Representation of T2a and T2b lung cancer. (Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2008 Aletta Ann Frazier, MD.)

even smaller size prompting many investigators to reexamine this question. Retrospective studies have shown that sublobar resection offers good overall survival for the very small (T1a) tumors. This has prompted a new randomized multi-institutional trial initiated by the Cancer and Leukemia Group B (CALGB 140503) to investigate the disease-free survival in patients with NSCLC less than or equal to 2 cm who undergo sublobar resection versus lobectomy.

The second issue concerns the value of extended mediastinal nodal dissections. Specifically, does the addition of a complete nodal dissection in a patient with no evidence of mediastinal nodal involvement confer any survival benefit? The American College of Surgeons Oncology Group (ACOSOG Z0030) trial investigated whether mediastinal lymph node dissection provided any benefit in lung cancer patients with T1 or T2 tumors, N0 or N1 disease, and no evidence of N2 disease based on intraoperative nodal sampling (1 to 2 nodes removed from each accessible nodal station) at the time of thoracotomy. Their initial findings revealed no increased risk associated with the addition of a complete nodal resection.[19] However, subsequent findings

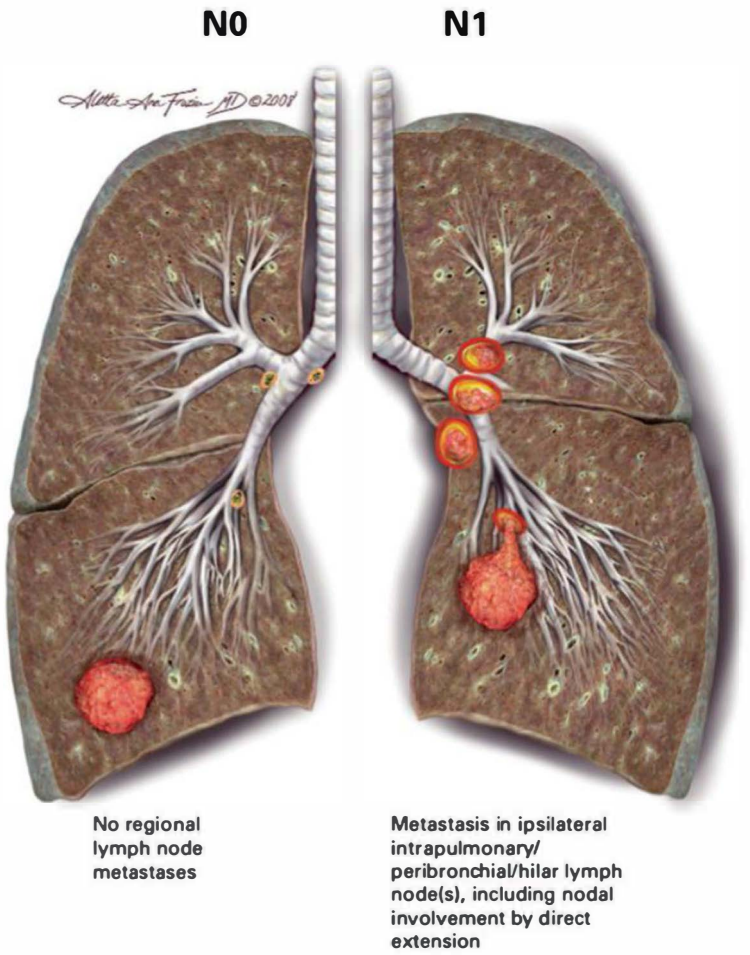



**FIGURE 9-4** Representation of N0 and N1 lung cancer. (Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2008 Aletta Ann Frazier, MD.)

revealed no difference in local and regional recurrence rates or survival between patients who received lymph node sampling and patients who received full mediastinal lymph node dissection.[20] Although the trial did not address the role of mediastinal lymph node dissection in patients with N2 disease, it did suggest that mediastinal lymph node sampling may be appropriate in patients with early-stage lung cancer.

## CHEMOTHERAPY

***Neoadjuvant Therapy.*** Neoadjuvant chemotherapy's role for stage I and II lung cancer was under investigation when studies demonstrating the effectiveness of adjuvant therapy were published. Unfortunately, these findings mandated the closure of the ongoing randomized trials of neoadjuvant chemotherapy for early-stage disease. Still, some clinical situations may derive benefit from a neoadjuvant course of chemotherapy. Dierpierre et al. found that while neoadjuvant therapy provided no overall survival advantage compared with surgery alone in patients with stage I and II lung cancer, neoadjuvant chemotherapy did shrink the tumor and thus facilitate lobectomy in patients who require pneumonectomy at disease onset.[21] His study showed that 62 percent of patients who received neoadjuvant chemotherapy had a decrease in the size of the tumor. A similar finding was seen in the Southwest Oncology Group Trial S9900, phase III study that looked at induction chemotherapy in early stage NSCLC.[22]

***Adjuvant Therapy.*** A meta-analysis performed by NSCLC collaborative group of early adjuvant chemotherapy trials showed that there was a trend toward benefit for patients who are given adjuvant platinum-based chemotherapy compared with patients who had surgery alone. There was a bsolute survival benefit of 5 percent over 5 years.[23] Subsequent trials have shown that adjuvant chemotherapy may benefit patients with resected pathologic stage II NSCLC and the benefits for stage IB were mixed. Staging was based on the 6th edition of the staging system. In patients with good

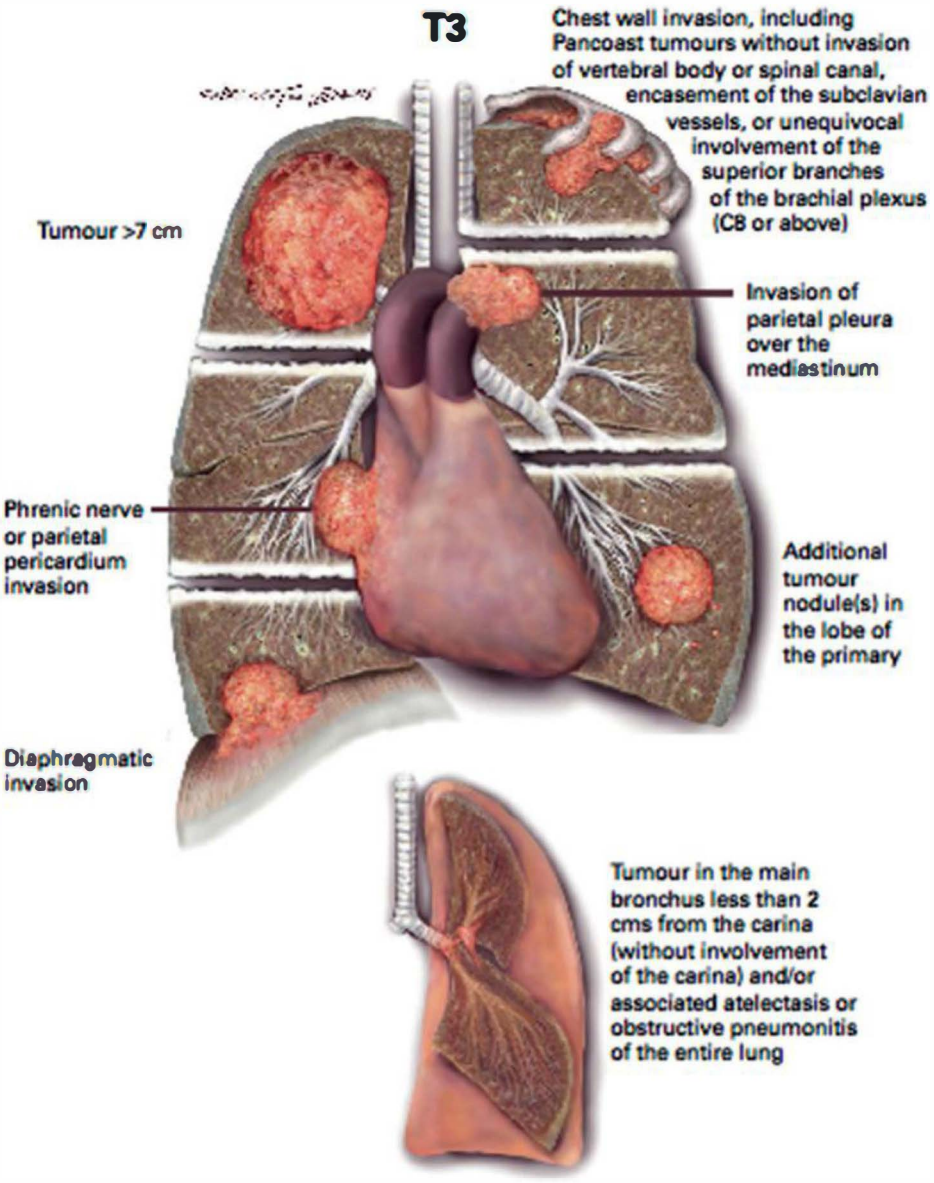



**FIGURE 9-5** Representation of T3 lung cancer. (Reprinted with permission courtesy of t he International Association for the Study of Lung Cancer. Copyright 2008 Aletta Ann Frazier, MD.)

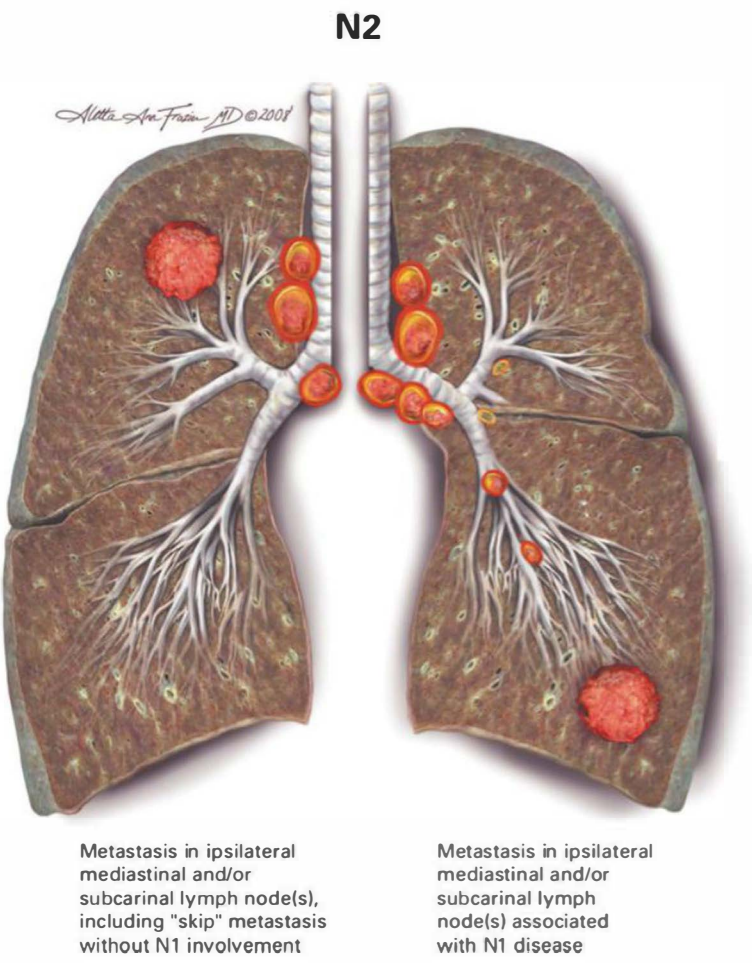



**FIGURE 9-6** Representation of N2 Lung Cancer. (Reprinted with permission courtesy of t he International Association for the Study of Lung Cancer. Copyright 2008 Aletta Ann Frazier, MD.)

performance status, adjuvant chemotherapy is begun within 2 months of curative resection. The most frequently studied adjuvant chemotherapy regimen for stage IB or II lung cancer is cisplatin plus vinorelbine for three or four cycles. Five trials have investigated the use of adjuvant chemotherapy after curative resection in lung cancer patients.

The Adjuvant Lung Project Italy enrolled 1209 patients who underwent curative resection for stage I–IIIA disease and were randomized to receive either placebo or mitomycin, vindesine, and cisplatin for three cycles. The study found no survival benefit with adjuvant chemotherapy. However, critics of the study felt the aggressive triple chemotherapy regimen and the high percentage of patients who received adjuvant radiotherapy (43%) led to the poor outcome in the adjuvant group and may explain the lack of benefit.[24]

Four trials have used cisplatin-based doublets; three were positive whereas one trial showed no difference. The International Adjuvant Lung Cancer Trial (IALT) randomized patients after curative surgery for stages I–IIIA lung cancer to two cycles of cisplatin-based chemotherapy or observation and found a 4 percent absolute increase in overall survival and a 5 percent absolute increase in disease-free survival in the chemotherapy arm.[25] The Adjuvant Navelbine International Trial Association (ANITA) trial, randomized 840 patients with completely resected pathologic stages I–IIIA to four cycles of cisplatin plus vinorelbine or observation and found a significantly higher survival rate in the treatment arm (51%) than in the observation arm (43%).[26] The National Cancer Institute of Canada Adjuvant Study randomized 482 patients with stages IB, IIA, or IIB lung cancer to either observation or treatment with cisplatin and vinorelbine and found markedly improved absolute survival of 15 percent in 5 years in the treatment arm.[27] Subset analyses suggested that the greatest benefit was derived in patients with stage II lung cancer and no benefit in stage IB patients. The role of adjuvant therapy in stage IB patient was studied in a simultaneously performed CALGB trial. CALGB 9633 enrolled

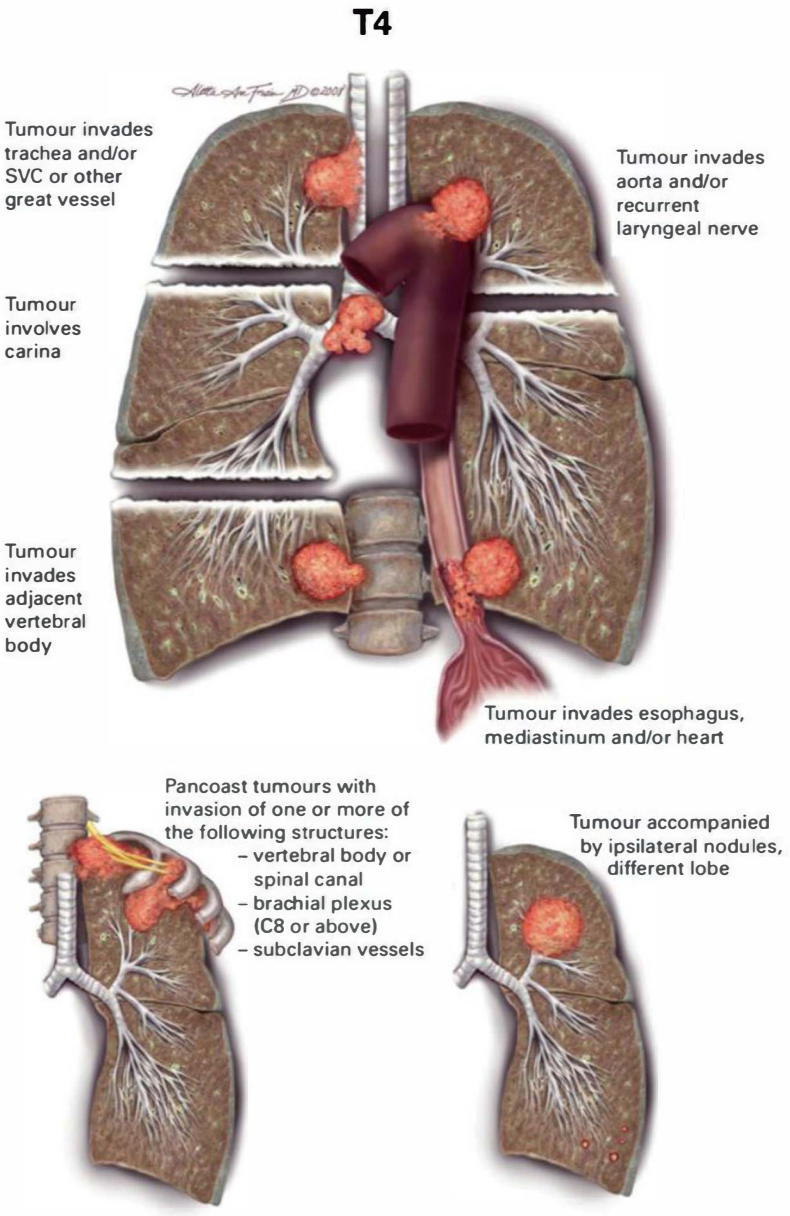



**FIGURE 9-7** Representation of T4 lung cancer. (Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2008 Aletta Ann Frazier, MD.)

344 pathologic stage IB patients and initially found a significant advantage conferred by the use of adjuvant paclitaxel and carboplatin. There was 12 percent absolute survival advantage in the adjuvant chemotherapy arm in 4 years. This finding led to an early closure of the trial. Unfortunately, when updated results were examined, there was no difference in overall survival between the observation arm and the arm that received adjuvant therapy.[28]

The use of adjuvant chemotherapy for completely resected stage II NSCLC should be strongly considered for all patients. Since the subset analyses and CALGB 9633 did not show a significant benefit for adjuvant chemotherapy in pathologic stage IB patients, most oncologists will consider its use only in selected cases such as very large tumors without nodal involvement. Conveniently, the new 7th edition of the staging system has restaged these larger tumors (previously staged IB in the old system) as IIA.

## RADIOTHERAPY

Radiotherapy plays no role in neoadjuvant therapy and plays only a small role in adjuvant therapy for patients with

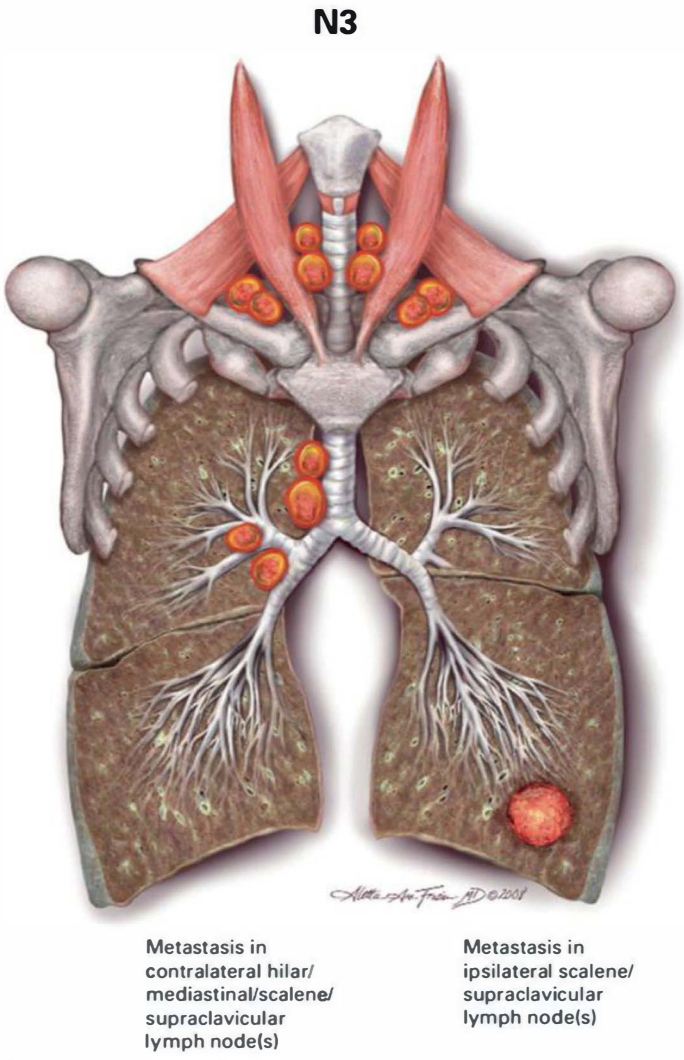



**FIGURE 9-8** Representation of N3 lung cancer. (Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2008 Aletta Ann Frazier, MD.)

stage I or II NSCLC who received an incomplete resection. However, radiotherapy should be considered as a potentially curative option in patients with locoregional disease who may not tolerate surgery because of poor performance status or poor pulmonary function.

***Definitive Radiotherapy for Surgery-Intolerant Patients.*** Generally, chemotherapy and high-dose radiotherapy are used to treat patients with early-stage lung cancer who are not surgical candidates. Standard radiotherapy includes three-dimensional conformal radiotherapy planning and delivery and/or intensity-modulated radiotherapy to limit the radiation dose to normal lung tissue. The Radiation Therapy Oncology Group (RTOG) recommends delivering 60 Gy of radiation in 30 fractions over 6 weeks.[29] Concurrent chemotherapy has been found to improve locoregional tumor control and patient survival although some toxicity is increased.[30]

***Definitive Radiotherapy for Surgery-Tolerant Patients.*** Stereotactic radiotherapy focuses ablative radiotherapy doses to the tumor with less toxicity to adjacent structures by treating only the tumor volume and a rim of surrounding tissue. Although the total dose delivered remains 60 Gy, large fractions of either 15 Gy over 4 fractions or 20 Gy over 3 fractions are used depending on tumor location. This high-dose low-fraction delivery provides a much higher biologic effective dose to the tumor compared with convention radiotherapy. Although only a small lung volume is treated, the local control rates are significantly higher than with conventional radiotherapy. These encouraging results have prompted an international randomized trial comparing

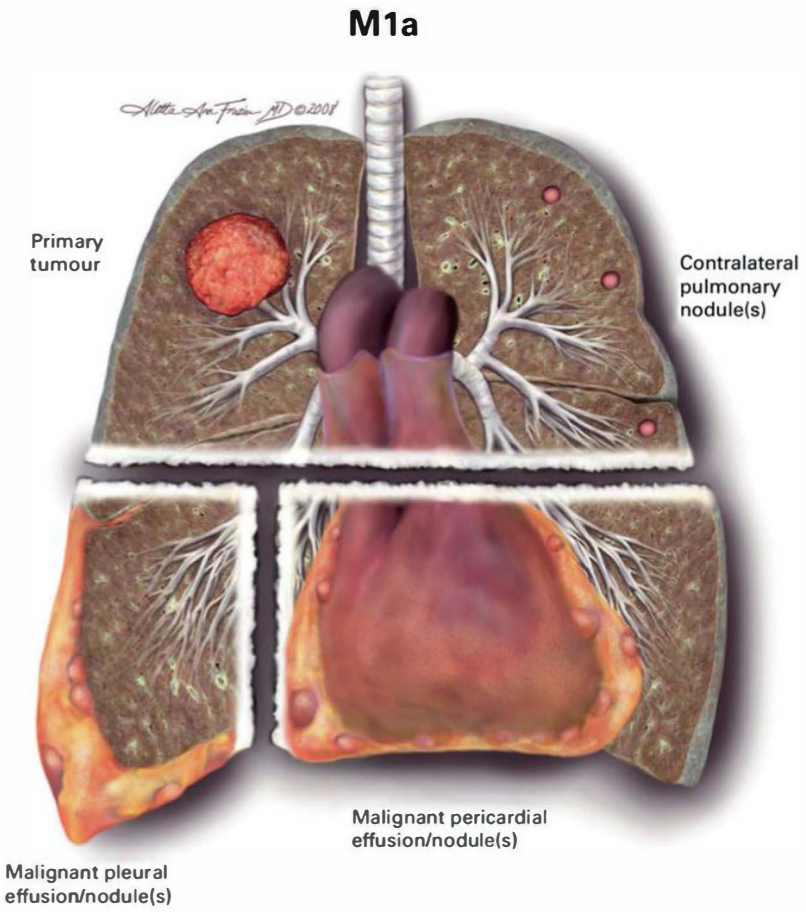



**FIGURE9-9** Representation of M1a Lung Cancer. (Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2008 Aletta Ann Frazier, MD.)

CyberKnife® stereotactic radiotherapy with surgical resection in stage I Nonsmall Cell Lung Cancer (STARS). The trial, to be completed by 2013, will examine survival as the primary endpoint.

***Neoadjuvant Radiotherapy.*** Neoadjuvant radiotherapy has no role in the treatment of patients with stage I or II NSCLC.

***Adjuvant Radiotherapy.*** Adjuvant radiotherapy is recommended only for NSCLC patients with positive surgical margins who cannot tolerate additional pulmonary resection.

## Stage IIIA Nonsmall Cell Lung Cancer

A multimodal approach should be used to treat patients with stage III NSCLC. Patients with unresectable (bulky or multistation) N2 disease should receive definitive chemoradiotherapy. Patients with resectable N2 disease have additional options. One approach is to begin with two to four cycles of neoadjuvant chemotherapy followed by restaging. In the absence of any progression, a complete resection should be performed and if N2 disease persists, radiotherapy can be administered to decrease local and regional recurrences. An alternative strategy is to begin with induction chemoradiation therapy followed by restaging and surgical resection. Finally, if the risk of surgery is deemed to be great (comorbidities, the need for a pneumonectomy, etc.), then definitive chemoradiation therapy can be offered.

### UNRESECTABLE STAGE IIIA DISEASE—N2

Patients with unresectable stage IIIA disease should be treated with definitive chemoradiotherapy. Van Dermmek et al. evaluated patients with unresectable N2 disease at presentation and found that the disease rarely became resectable following neoadjuvant chemoradiotherapy and surgery provided no overall survival benefit.[31]

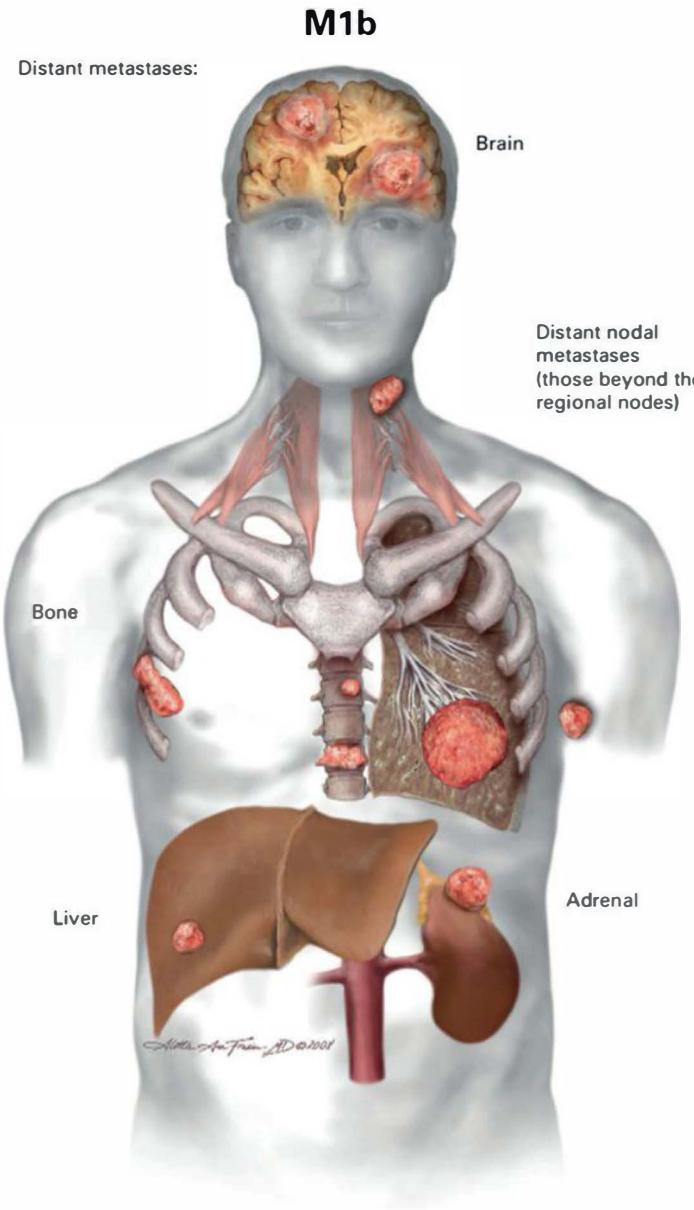



**FIGURE 9-10** Representation of M1b lung cancer. (Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2008 Aletta Ann Frazier, MD.)

## RESECTABLE STAGE IIIA DISEASE—N2

Two strategies are generally used to treat patients with resectable stage IIIA disease. One strategy involves neoadjuvant chemotherapy, and the other strategy involves neoadjuvant chemoradiotherapy.

***Neoadjuvant Chemotherapy, Surgery, and Adjuvant Radiotherapy.*** Roth et al.[32] and Rosell et al.[33] found that neoadjuvant chemotherapy plus surgery impart a survival advantage over surgery alone in patients with stage IIIA disease. However, both studies have been criticized for having a small number of patients, no requirement for pathologic nodal staging, and, in the Rosell study, poorer-than-expected outcomes in the surgery-only group. However, despite these criticisms both studies have continued to remain positive even at late reanalysis. The benefit of adjuvant radiotherapy after neoadjuvant chemotherapy and subsequent surgery for patients with pathologic stage IIIA-N2 disease has also been reported separately and includes fewer local recurrences, fewer distant metastases,

**TABLE 9-2: Lung Cancer Stage Grouping**

| Occult carcinoma | TX | N0 | M0 |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1a, b | N0 | M0 |
| Stage IB | T2a | N0 | M0 |
| Stage IIA | T2b | N0 | M0 |
| | T1a, b | N1 | M0 |
| | T2a | N1 | M0 |
| Stage IIB | T2b | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T1a, b, T2a, b | N2 | M0 |
| | T3 | N1, N2 | M0 |
| | T4 | N0, N1 | M0 |
| Stage IIIB | T4 | N2 | M0 |
| | Any T | N3 | M0 |
| Stage IV | Any T | Any N | M1 |

Data from *TNM Classification of Malignant Tumours*, 7th Edition, (eds): L.H. Sobin and Ch. Wittekind. Copyright 2009 Wiley, New York.

and longer survival than patients who do not receive adjuvant radiotherapy.[34]

***Neoadjuvant Chemoradiotherapy and Surgery.*** At the same time investigators were examining the impact of neoadjuvant chemotherapy for stage IIIA NSCLC other investigators were evaluating the benefit of neoadjuvant chemoradiotherapy followed by surgery compared with surgery alone. Early results appeared promising with survival advantages similar to those seen in the Roth and Rosell studies.[35] Close examination of this data suggested that a new question centered on the additional benefit surgery offered beyond definitive chemoradiotherapy. This prompted a subsequent CALGB trial to see if surgery provided additional benefit for this stage. The study initiated chemoradiotherapy and after completing a preoperative dose of radiotherapy patients were quickly restaged. If there was no progression, patients were randomized to surgery or completion of definitive radiotherapy. The trial began in 1993 and due to slow accrual was finally stopped short of its planned enrollment and published in 2009. Albain et al. found no difference in survival between patients with resectable N2 disease who were treated with neoadjuvant chemoradiotherapy and surgery and patients with resectable N2 disease who were treated with definitive chemoradiotherapy alone. However, a subset analysis of patients in the surgery group revealed that neoadjuvant chemoradiotherapy imparted a survival advantage in patients who underwent lobectomy but no survival advantage in patients who underwent pneumonectomy. Pneumonectomy after chemoradiotherapy was associated with a very high mortality and this increased surgical risk appeared to erode any oncologic benefit derived by the addition of surgery in these patients.[36] Most investigators will therefore still offer surgery after chemoradiotherapy if the tumor resection can be accomplished with a lobectomy. If a pneumonectomy is possible neoadjuvant chemotherapy may be a better alternative.

### STAGE IIIA—T4 N0/N1

Invasion of the carina, superior vena cava, vertebral body, heart, great vessels, and esophagus are considered to be T4 tumors. In these patients with N0/N1 status does seem to have survival advantage with radical surgical resection with negative margin and in the absence of N2 disease surgical resection should be offered is technically and physiologically feasible.[37] The role of neoadjuvant or adjuvant chemotherapy, although not rigorously investigated, does seem appropriate as an extrapolation of results from its use in IIIA disease. The benefit of adjuvant radiation therapy is determined on a case-by-case basis.

## Stage IIIB and IV Nonsmall Cell Lung Cancer

Chemotherapy is the main treatment for patients with advanced lung cancer. A platinum-based doublet is reported to achieve median survival duration of 9 months and an overall 1-year survival rate of 30 percent and is considered first-line therapy for these patients.[38] Targeted therapies may have the potential to cure patients with advanced disease. Local therapy, when appropriate, is performed with radiotherapy.

### CHEMOTHERAPY

***First-Line Chemotherapy.*** Chemotherapy is the mainstay of therapy for stages IIIB and IV disease. Surgery and radiotherapy do not provide significant benefit in this setting. The first-line regimen is a platinum-based doublet such as cisplatin or carboplatin plus docetaxel, paclitaxel, or vinorelbine. Cisplatin and carboplatin trigger apoptosis by crosslinking DNA. Docetaxel and paclitaxel are antimitotic agents that stabilize the microtubule assembly to cause apoptosis. Vinorelbine, also an antimitotic agent, inhibits microtubule depolymerization and triggers apoptosis. Patients with nonsquamous cell histology, no brain metastasis, no significant hemoptysis, and good performance status may benefit from the addition of bevacizumab, an antiangiogenic agent.[39]

***Second-Line or Additional Chemotherapy and Targeted Agents.*** If a patient fails first-line therapy, additional chemotherapy using new agents can be administered based on the patient's status and tumor type. In addition, there are now targeted biologic agents that may be used to treat this group of patients. Erlotinib, an EGFR tyrosine kinase inhibitor, is considered a secondary agent for patients in whom first-line therapy for stage IIIB or IV NSCLC has failed.[40] In one study, patients who received erlotinib had significantly longer progression-free period (2.2 months vs. 1.8 months) and overall survival (6.7 months vs. 4.7 months)

than patients who received placebo. Rash and diarrhea were the two most common side effects of erlotinib. Erlotinib has not shown benefit in patients with K-RAS mutations but it has been found to be effective among patients with high numbers of EGFR gene copies and mutations.[40] In addition, pemetrexed, which inhibits the formation of precursor purine and pyrimidine nucleotides, has been approved for second-line therapy.

### RADIOTHERAPY

***Treatment of Stage IIIB Disease.*** Patients with stage IIIB disease are often treated with concomitant chemoradiation therapy as a curative approach although the 5-year survival for patients with documented stage IIIB disease treated in this manner is 15 percent.[41]

***Treatment of Stage IV Disease.*** The role of radiotherapy in patients with advanced NSCLC is limited to the palliation of symptoms that include superior vena caval obstruction, hemoptysis, neurologic symptoms, and chest, shoulder, arm, and bone pain. Radiotherapy does not effectively relieve bronchial obstruction from atelectasis or vocal cord paralysis due to tumor invasion of the phrenic or recurrent laryngeal nerve. Radiotherapy has been shown to improve symptoms stemming from metastatic disease in the brain and bones and can also reduce or eliminate paraneoplastic syndromes, especially those caused by adrenocorticotropic hormone and antidiuretic hormone overproduction.

Radiation pneumonitis is a potential side effect of radiotherapy in patients with advanced NSCLC. A single radiation dose of 8 to 10 Gy can damage normal lung tissue. The concurrent use of chemotherapeutic agents such as bleomycin, dactinomycin, carmustine, cyclophosphamide, and methotrexate increases the side effects of radiotherapy. Radiation pericarditis occurs in up to 5 percent of patients. Dysphagia caused by radiation-induced inflammation of the esophagus, which rarely leads to obstruction and often resolves after a short period of time, may also occur. The most serious complications of radiotherapy are myelopathy and Brown–Sequard syndrome.

### SURGERY

***Treatment of Stage IV—Oligometastasis to the Brain or Adrenals.*** Surgery has been reported in two unique presentations of stage IV disease. Retrospective studies have demonstrated long-term improvement in survival for patients with surgically resected localized lung cancer and a solitary metastasis to the brain or the adrenal compared with the historical survival of stage IV patients. In lung cancer patients with a solitary brain metastasis, aggressive resection of the lung, and metastasis followed by whole-brain irradiation is offered if the morbidity and mortality associated with the treatment is acceptable. In this nonrandomized study, patients who underwent definitive treatment at both sites had an overall median survival of 26 months, whereas patients who did not receive definitive therapy had overall survival duration of 13 months.[42] In NSCLC patients with isolated adrenal metastasis, the adrenal mass and primary lung cancer should be resected if possible.[43] The 5-year survival rate among patients who undergo resection of both the primary tumor and adrenal mass is 26 percent.[44]

## Special Tumors

### SMALL CELL LUNG CANCER

Patients with limited small cell lung cancer should receive locoregional and prophylactic cranial radiotherapy in addition to chemotherapy. Patients with primary tumors less than 5 cm for whom mediastinoscopy is negative may benefit from a lobectomy with mediastinal lymph node dissection. Patients with large tumors or any lymph node involvement should receive chemotherapy and mediastinal radiotherapy.[45] Chemotherapy is the main treatment for patients with extensive small cell lung cancer.

### PANCOAST TUMORS

Pancoast tumors, which are located at the apical pleuropulmonary groove (superior sulcus), are very difficult to resect because they often involve the vertebral bodies, brachial plexus, and subclavian vessels. Optimal management of these complex tumors does not yet exist. An investigation of the multimodal treatment of Pancoast tumor showed a reasonable survival rate with neoadjuvant chemoradiotherapy and surgery. Patients with T3-4, N0-1 Pancoast tumors received two cycles of cisplatin and etoposide plus 45 Gy of concurrent radiation. Patients were restaged after neoadjuvant therapy; patients who did not have distant metastasis or local progression underwent resection and adjuvant chemotherapy. Patients treated in this fashion had an overall 5-year survival rate of 44 percent. The study showed that a multimodal approach to treating patients with Pancoast tumors is feasible and results in a high rate of complete resection and complete response.[46] An alternative approach was described for Pancoast tumors with vertebral involvement. These patients were treated with surgery followed by adjuvant chemoradiotherapy and had an overall 5-year survival rate of 27 percent.[47]

# SURGICAL THERAPY

## Preoperative Assessment

With any major surgical procedure, one must perform careful assessment of preoperative status to reduce postoperative risks. Accurate assessment of patient's nutritional status, coagulation profile, hemoglobin level, renal function, and hepatic function can provide better understanding of patient's status. In addition to basic factors, it is crucial that

patient undergoes the pulmonary and cardiovascular assessment prior to any surgical resection.

### PULMONARY ASSESSMENT

The most important presurgical evaluation for lung cancer patients is the pulmonary function test. If the forced expiratory volume in 1 s ($FEV_1$) and carbon monoxide diffusion capacity (DLCO) are greater than 80 percent of the predicted values, the patient can tolerate up to a pneumonectomy. However, if the $FEV_1$ and DLCO are below the 80 percent threshold, then the predicted postoperative value of lung function should be assessed by counting the number of segment remaining after removal of the tumor. The right upper lobe has three segments, the right middle lobe has two segments, the right lower lobe has five segments, the left upper lobe has four segments, and the left lower lobe has four segments. For example, if left lower lobectomy is planned then 14 segments (18 segments − 4 segments) or 77.8 percent (14/18) of the lung will be still available postoperatively. For a patient with a preoperative $FEV_1$ of 60 percent, the postoperative predicted value would be 77.8 percent of 60 percent or 47 percent $FEV_1$.[48]

For patients with obstructing tumors resulting in segmental/lobar/or pneumonic collapse, this estimate is no longer adequate since the segments that will be removed are no longer contributing effectively to the patient's overall pulmonary function. A similar situation is seen when resecting lung that is significantly damaged secondary to emphysema. For these patients, measuring the percentage of perfusion and ventilation in the part of the lung to be resected provides a more accurate measure of postoperative lung function. For example, if a tumor involves the distal left lower lobe, bronchus, and pulmonary artery in a patient with an $FEV_1$ of 45 percent, and the perfusion rate is only 5 percent in that lobe, the patient will have an $FEV_1$ of 43 percent after resection or 95 percent of 45 percent.

The usual thresholds above which the planned resection can be performed without a significant increase in perioperative mortality is a postoperative predicted $FEV_1$ and DLCO of 40 percent. When the postoperative predicted values are just above or below 40 percent patients should undergo cardiopulmonary exercise testing to determine whether surgery is appropriate. Patients with a maximal oxygen consumption ($Vo_2$ max) of >15 mL/kg/min are not at an increased risk of complication or death following resection. However, patients with a $Vo_2$ max of <10 mL/kg/min are at a significantly higher risk of complications or death and are not surgical candidates. Patients with a $Vo_2$ max of between 10 and 15 mL/kg/min should undergo pulmonary rehabilitation. Pulmonary function should be reassessed periodically to determine whether these patients are candidates for pulmonary resection.

One exception to this rule is the patients with emphysema. Patients with poor pulmonary function and heterogeneous emphysema with upper-lobe predominance who develop a tumor in the upper-lobe may benefit from lung volume reduction surgery (LVRS) along with the resection of the lung cancer. The criteria for patients who can tolerate LVRS are an $FEV_1$ of <40 percent, a DLCO >20 percent, total lung capacity >120 percent, and residual lung volume >150 percent.[49] Rigorous pulmonary rehabilitation is necessary in patients who are going to undergo LVRS.

### CARDIAC WORK-UP

Patients must have adequate cardiac function to tolerate pulmonary resection. Cardiac work-up including an EKG, a detailed history, and an echocardiogram or a stress test, when indicated, should be performed to ensure that patients can tolerate lung resection. Coronary artery disease is cardiac significant risk factor for myocardial infarction following lung resection. The likelihood of myocardial infarction following resection in patients without coronary artery disease is <0.5 percent, while the likelihood of myocardial infarction following resection in patients with coronary artery disease is about 6 percent.[50]

Arrhythmias are also very common postoperatively and any preexisting arrhythmias will place patients at an even higher risk.

## Technical Considerations

Although posterior lateral thoracotomy with entry through the fifth intercostal space remains the standard incision for anatomic pulmonary resections, complete resections can also be performed through posterior muscle-sparring, anterior muscle-sparing and axillary thoracotomies as well as VATS using two, three, or four incisions. The main advantages of VATS over traditional thoracotomy are reduced postoperative pain, earlier return to normal activity, and an increased likelihood of patients receiving adjuvant chemotherapy.

Upon entry into the thoracic cavity, the surgeon reassesses the clinical stage of the tumor. If there is pleural effusion that is positive for malignancy on cytologic evaluation or if the tumor is invading structures that cannot be resected, the surgeon aborts the surgery. The entire lung and parietal pleura are then inspected and palpated for additional masses. Any suspicious nodules located in lobes other than the tumor bearing lobe are biopsied and the specimens cytologically evaluated; if the nodules are positive for malignancy, the surgeon aborts the surgery. If there are malignant-appearing, broad-based, or dense adhesions to the chest wall the surgeon determines whether the tumor can be resected with negative margins. If the tumor is deemed resectable, the surgeon divides the inferior pulmonary ligament and renders the lung completely atelectatic.

The pulmonary vessels are now dissected along the plane of Leriche. This perivascular plane may be absent in the presence of long-standing granulomatous or tuberculous disease, after major chemotherapy or thoracic radiotherapy, and in cases of reoperation. In these situations, proximal

control of the main pulmonary artery and the two pulmonary veins may be necessary before the more peripheral arterial dissection can be started. During an open operation the pulmonary arterial and venous branches can be ligated in any order. Although there is theoretical concern of pulmonary congestion when the pulmonary vein is ligated first, other collateral vessels between the lobes usually compensate adequately. During a VATS lobectomy the order in which vessels are ligated is more defined with the pulmonary vein often taken first.

Bronchial exposure should not involve stripping the bronchial surface of its adventitia. Aggressive dissection may compromise the vascular supply of the bronchus and lead to impaired healing and bronchial dehiscence. Overlying nodal tissues should be cleared, and major bronchial arteries should be clipped just proximal to the point of division. Bronchial closure has been greatly facilitated by the use of automatic staplers. With the stapler applied but not yet fired, the remaining lung should be ventilated to determine whether there is any impairment of ventilation secondary to stapler placement too close to a proximal lobar bronchus. Only when the absence of ventilatory impairment has been confirmed should the stapler be fired. When bronchial length is limited, the surgeon may perform suture closure of the bronchial stump rather than attempting to force a stapler around the bronchus. A vascularized rotational tissue flap should be used to reinforce the bronchial closure whenever there is a high risk of bronchial stump dehiscence such as in the presence of active infection, steroids, chemotherapy, radiation, or poor nutritional status.

## Right Lung

### RIGHT HILAR DISSECTION

First, the lung is then rotated posteriorly, and the pleura is incised posterior to the course of the phrenic nerve, which usually passes close to the base of the superior pulmonary vein. The phrenic nerve is carefully and gently mobilized anteriorly to expose the superior pulmonary vein and inferior pulmonary vein. Next, the right upper lobe is then rotated more inferiorly to provide a better view of the superior aspect of the hilum and allow complete exposure of the truncus anterior branch. Finally, the lung is rotated anteriorly, and the right main bronchus, right upper-lobe bronchus, and right bronchus intermedius are exposed.

### RIGHT PNEUMONECTOMY

After hilar dissection, the lung is rotated inferiorly and posteriorly, and the main trunk of the right pulmonary artery is exposed as it exits the pericardium posterior to the vena cava. The ligation and division of the right pulmonary artery can be accomplished using a vascular stapler or dividing the vessel between clamps and oversewing with 3-0 nonabsorbable sutures. Next, the lung is rotated posteriorly, and the superior pulmonary vein is mobilized on its superior and inferior aspects with blunt and sharp dissection then encircled, ligated, and divided using a vascular stapler. Division between clamps and oversewing with 3-0 nonabsorbable sutures is also acceptable. The lung is then retracted superiorly, and the inferior pulmonary vein is dissected, ligated, and divided in the same manner as the superior pulmonary vein.

After dividing the major vessels, the lung is retracted anteriorly and the subcarinal lymph nodes are mobilized. The bronchial artery originates at the apex of the carina anteriorly and should be clipped. The remaining peribronchial tissues are then mobilized distally with blunt and sharp dissection so that the bronchus is exposed within 1 cm of the carina. A tick tissue stapler is oriented so as to approximate the anterior cartilaginous and posterior membranous walls and the bronchus is divided distal to the staple line. On the right side, the coverage of the pneumonectomy stump with viable tissue is preferred, especially if the patient has received or will receive chemotherapy and/or radiotherapy. The ideal tissue for coverage is either a rotated intercostal muscle flap harvested during entry into the chest or a pericardial fat pad rotational flap. The flap is secured with carefully placed 4-0 polypropylene sutures.

### RIGHT UPPER LOBECTOMY

Two branches of the pulmonary artery—the truncus anterior and posterior ascending arteries—enter the right upper lobe. The truncus anterior is the first branch of the right main pulmonary artery and is typically a large branch that immediately bifurcates into two or three branches. Once the truncus anterior is exposed, it is either suture-ligated and divided or transected with a vascular stapler. The posterior ascending artery typically originates from the interlobar pulmonary artery opposite the right middle lobe branch. To expose the posterior ascending pulmonary artery, the interlobar fissure is dissected, and the pulmonary artery is exposed at the junction of the major and minor fissures. All the branches are dissected including the middle lobe, posterior ascending, superior segmental, and basilar segmental arteries. The posterior ascending artery is often partially obscured by a level 11 interlobar lymph node and the posterior segmental branch of the superior pulmonary vein, which traverses the fissure towards the superior pulmonary vein. If the exposure is adequate, the posterior ascending branch can be ligated and divided or stapled. If the exposure proves difficult completion of the fissure between the upper lobe and lower lobe can sometimes facilitate this exposure. This is facilitated by dividing the pleura in the posterior hilum along the lateral edge of the bronchus intermedius. A level 11 lymph node located between the right upper-lobe bronchus and the bronchus intermedius is then removed to allow exposure of the posterior ascending branch of the pulmonary artery. A right-angle clamp can be passed from the interlobar fissure between the superior segmental branch of the pulmonary artery and the posterior ascending pulmonary artery to the

posterior hilar dissection. The fissure can then be completed with either a medium or thick tissue stapler.

Next, the superior pulmonary vein is dissected, and the upper- and middle-lobe branches are carefully identified. The branches draining the upper lobe are then ligated and divided or stapled. Attention is now turned to completion of the minor fissure. Dissection continues along the lateral surface of the pulmonary artery until the right middle-lobe artery is identified. A right-angle clamp can be passed from this location posteriorly to the interlobar dissection. The minor fissure is then completed through the serial application of thick tissue staplers.

The upper lobe is retracted superiorly and posteriorly, and the pulmonary artery is gently retracted anteriorly. The bronchus is circumferentially exposed to the right upper lobe, and all nodal tissue surrounding the right upper-lobe bronchus is swept distally so that it can be included with the specimen. Once an adequate length of the right upper-lobe bronchus is exposed, the lung is rotated anteriorly to allow visualization of the course of the bronchus intermedius. The right upper lobe bronchus is compressed within with a thick tissue stapler and the right lung is ventilated to confirm that the bronchus intermedius has not been compromised. Once confirmed, the stapler is fired and the bronchus is divided distally.

### RIGHT MIDDLE LOBECTOMY

The initial steps in a right middle lobectomy can begin with the interlobar dissection described above. There can be one dominant or two smaller middle-lobe arteries. Once the anatomy has been confirmed, the arterial branches to the middle lobe can be individually ligated and divided. If additional exposure is needed before ligation, the minor fissure can be completed to yield added exposure of a proximal middle-lobe artery. Once the arteries are divided, the lung is rotated posteriorly to expose the superior pulmonary vein. The branches to the upper and middle lobes are carefully identified, and the branches to the middle lobe are ligated and divided. The minor fissure is completed as described above. Once complete, the surgeon will have a clear view of the posterior segmental branch of the superior pulmonary vein and the interlobar pulmonary artery coursing posterior and medial to the veins. The fissure between the right middle and lower lobe can be completed using serial application of the thick tissue staplers by keeping the right middle lobe bronchus superiorly and the right lower lobe with the basilar branches of the pulmonary artery and the right lower-lobe bronchus inferiorly.

The middle lobe is then rotated superiorly and posteriorly to expose the right middle-lobe bronchus, which usually arises anterior and inferior to the right middle-lobe branches of the pulmonary artery. The basilar arterial branches to the right lower lobe are gently mobilized posteriorly to expose the bronchus intermedius and the origin of the right middle-lobe bronchus. Peribronchial lymph nodes located in this region should be dissected and removed, with care taken not to injure the bronchial arterial branches. Once the bronchus is free, it is divided and either oversewn or stapled.

### RIGHT LOWER LOBECTOMY

Once again, the interlobar pulmonary artery and its branches are exposed in the major fissure. The pulmonary branches to the superior segment and the basilar segments of the right lower lobe, posterior ascending branch of right upper lobe, and right middle lobe branches are identified. The superior segmental and basilar segmental artery is encircled, ligated, and divided. Next, the fissure between the lower lobe and upper lobe is completed as described above for a right upper lobectomy. Next, the inferior pulmonary vein is then encircled as it exits the pericardium. This step is facilitated by the dissection of the superior edge of the inferior pulmonary vein with the lung rotated first anteriorly and then posteriorly. Once encircled, the pulmonary vein is divided with a vascular stapler. Then, the basilar segmental bronchi and the middle-lobe bronchus are exposed allowing division of the fissure between middle lower lobes. The removal of lymphoid tissue facilitates the application of stapler.

Level 11 and 12 lymph nodes are cleared distally along the bronchi to expose the origin of the superior segmental bronchus. The lung is then rotated anteriorly, and the bronchus intermedius is dissected distally until the origin of the superior segmental bronchus is identified. The branch of the inferior pulmonary vein draining the superior segment of the right lower lobe should be mobilized distally to allow adequate exposure of the origin of the superior segmental bronchus. The superior segmental bronchus is encircled, divided, and oversewn or stapled. Next, the basilar segmental bronchi are encircled at a point where closure will not affect airflow to the middle-lobe bronchus. Appropriate placement is confirmed by ventilating the right lung while the stapler or clamp is applied to the base of the basilar bronchi. If placement is adequate, the basilar segmental bronchi are divided and sewn or stapled.

## Left Lung

### LEFT HILAR DISSECTION

Retract the lung anteriorly and open the hilar pleura to expose the inferior pulmonary vein, and continue superiorly to expose the left main bronchus and the pulmonary artery. Next, with the lung retracted inferiorly, the pleura is incised under the arch of the aorta to expose the left main pulmonary artery. A variable number of small vessels and vagal branches to the lung are encountered and can be ligated and divided. Care is taken not to injure the recurrent laryngeal nerve as it branches from the vagus nerve and courses under the arch just posterior to the ligamentum arteriosum. With the lung now retracted posteriorly, the hilar pleura is opened parallel to and posterior to the course of the phrenic nerve, exposing the main trunk of the left pulmonary artery and the superior pulmonary vein.

### LEFT PNEUMONECTOMY

The superior and posterior surfaces of the main trunk of the pulmonary artery are dissected as it enters the thorax under the aortic arch. Once the perivascular space is entered, the entire vessel can be encircled with blunt dissection. If the superior pulmonary vein limits access to the anterior surface of the pulmonary artery, it may be ligated and divided first to facilitate arterial exposure. Once the pulmonary artery is encircled, the vessel can be divided using vascular stapler or between clamps.

Next, with the lung retracted posteriorly, the superior pulmonary vein is identified, encircled with blunt dissection, and then ligated and divided. The lung is then retracted superiorly to expose the inferior pulmonary vein. Dissection is performed on the anterior and posterior aspects of the inferior pulmonary vein, and blunt dissection is used to completely encircle the vein after which it is ligated and divided. Finally, the lung is retracted anteriorly and superiorly. Complete dissection of the subcarinal lymph nodes is performed and facilitated by dividing one or two pulmonary branches of the left vagus nerve and both bronchial arteries. Gentle traction in conjunction with blunt dissection is applied to allow encirclement of the proximal left mainstem bronchus. An effort should be made to encircle the bronchus within 1 cm of the carina. A thick tissue stapler is then passed around the left main stem bronchus and applied within 1 cm of the carina. If the patient has a left-sided double-lumen tube, ensure that it is pulled back proximal to the carina. The stapler is fired, and the bronchus is divided distal to the staple line. Frequently, the position of the bronchial stump under the aortic arch deep within the mediastinum renders coverage of the stump unnecessary.

### LEFT UPPER LOBECTOMY

The interlobar fissure is developed with a combination of sharp and electrocautery dissection. The posterior aspect of the fissure between the apicoposterior segment of the left upper lobe and the superior segment of the left lower lobe is completed with cautery or GIA stapler to expose the proximal portion of the interlobar pulmonary artery. The left upper lobe is then retracted anteriorly and superiorly to expose the arterial branches supplying the upper lobe. This anatomy varies among patients. Although there are usually three branches—the apico-anterior, posterior, and lingular pulmonary arteries to the left upper lobe—there may be as many as seven vessels. Each vessel should be identified and individually ligated and divided. Although the superior and posterior branches are easily dissected, the anterior-most branch is frequently obscured by an apical branch of the superior pulmonary vein. Division of this venous branch may improve exposure and facilitate control of the arterial branch.

The superior pulmonary vein can then be easily identified in the anterior hilum. If the apical branch was not previously ligated, the surgeon should make every effort not to damage the pulmonary artery branches that lie posterior to this portion of the vein. The majority of the superior pulmonary vein lies anterior to the left upper-lobe bronchus. Once this vein is encircled, it is ligated and divided. The fissure between the lingula and the lower lobe is now completed with serial application of tissue staplers. The left upper-lobe bronchus is encircled and either clamped or ligated with a thick tissue stapler. To prevent inadvertent injury, the pulmonary artery branches to the lower lobe should be gently retracted posteriorly during stapler placement. With the stapler clamped, the left lung is ventilated to verify that air is flowing freely to the entire left lower lobe, and the left-sided double-lumen tube is moved to ensure that the tube is not in the stapler. The stapler is then fired, and the bronchus is divided distal to the staple line.

### LEFT LOWER LOBECTOMY

Dissection begins again within the interlobar fissure. The pulmonary artery is identified, and the branches to the upper and lower lobes are dissected. The superior segmental artery is encircled, ligated, and divided. The basilar segmental arteries are then encircled distal to the origin of the lingular artery and ligated and divided, with care taken to preserve blood flow to the lingular artery. The anterior and posterior fissures are identified and divided with tissue stapler. The lung is rotated superiorly to expose the inferior pulmonary vein. Once the vein is encircled, it is ligated and divided. Attention is then redirected to the interlobar fissure, and the left lower-lobe bronchus is identified. The origin of the bronchus is cleared by dissecting nodal tissue distally with blunt and sharp dissection. The upper-lobe branches of the pulmonary artery are gently retracted superiorly to allow placement of a tick tissue stapler on the bronchus. With the stapler clamped, the anesthesiologist ventilates the left lung to confirm the adequacy of airflow to the upper lobe, and that the stapler is not entrapping the double-lumen tube. The stapler is fired and the bronchus is divided distal to the staple line.

## Complications

### HIGH CHEST TUBE OUTPUT

A chest tube is placed after surgical resection to prevent symptomatic pleural effusion. The amount of pleural fluid output over a 24-h period that is considered safe to allow removal of the tubes has long been debated. However, a single-institution retrospective series recently found that symptomatic pleural effusion occurred after chest tube removal in just 11 of 2077 patients (0.55%) who had their chest tube removed for <450 mL of nonchylous drainage per day.[51]

### PERSISTENT AIR LEAK

Persistent air leak is defined as an air leak that occurs for at least 5 days following surgery. The incidence of persistent air leak is about 10 percent for patients who are undergoing lobectomy based on the Society of Thoracic Surgery

general thoracic surgery database that looked at 4979 cases.[52] A significantly smaller incidence of air leak of 3.2 percent was reported in a single-institution retrospective series when patients undergoing segmentectomy or wedge resections were mixed with lobectomy patients. In that series, the patients with a persistent air leak whose lung remained expanded off suction were discharged with their chest tube in place. At follow-up on an average of 16 days later, 57 of the 199 patients (28%) had persistent air leak and/or pneumothorax. All patients' chest tubes were eventually removed during follow-up. Over the next 3 months, air leaks resolved in all but three patients, who developed empyema.[53]

### PNEUMONIA

About 10 percent of patients develop pneumonia after undergoing pulmonary resection. Pneumonia carries a mortality rate of 19 to 26 percent following lung resection.[54,55] For patients who are undergoing pneumonectomy, pneumonia-associated mortality rates are 40 percent and smoking within 1 month of the operation increases the risk of developing pneumonia nearly threefold.[56] Pneumonia usually develops 2 to 4 days after surgery. Bronchial colonization, male gender, and chronic obstructive pulmonary disease are independent predictors of postoperative pneumonia. Standard treatments used to prevent pneumonia after lung resection includes prophylactic antibiotics, chest physiotherapy to clear secretions, bronchodilator placement, effective pain control, and early ambulation. The standard treatment for postoperative pneumonia is broad-spectrum antibiotics followed by targeted antibiotics selected on the basis of culture results. Repeated bronchoscopies can also be used to facilitate clearance of secretions

### ATRIAL FIBRILLATION

Atrial fibrillation is a common complication following pulmonary resection. The incidence of supraventricular arrhythmias following pulmonary resection is 10 to 28 percent. Although the cause of atrial fibrillation is unclear, contributing factors may include postoperative inflammation, right heart strain owing to right ventricular dilatation, pulmonary hypertension, and/or increased right heart pressures. Alternative explanations include conduction abnormalities from ligation of the pulmonary veins that contain the atrial fibers. The incidence of postoperative atrial fibrillation increases with the amount of lung tissue resected. Patients who undergo pneumonectomy are at the higher risk of developing atrial fibrillation. Curtis et al. found that postoperative supraventricular arrhythmias developed in 46.1 percent of patients who underwent pneumonectomy but only 14.3 percent of patients who underwent lobectomy.[57] Age is the second most important risk factor associated with development of atrial fibrillation. In addition to amount of lung resected and advancing age, male gender, history of congestive heart failure, and history of arrhythmias are risk factors for postoperative atrial fibrillation.[58] Atrial fibrillation often occurs in the first 24 to 72 h following thoracotomy. Although patients who develop atrial fibrillation frequently have a higher incidence of other complication,[59] the atrial fibrillation is usually controlled with medical therapy that is typically discontinued within 4 to 6 weeks of surgery.[60]

### EMPYEMA AND BRONCHOPLEURAL FISTULA

Empyema occurs in 1 to 2 percent of patients after lobectomy and 2 to 12 percent of patients after pneumonectomy. The management of postoperative empyema depends on the timing of its onset, the stability of the patient, and the presence of a bronchopleural fistula. If a bronchopleural fistula develops within the first 2 days after resection, the best option may be an additional surgery that includes debridement of the stump, reclosure at the healthy bronchus, and placement of a muscle flap. The stump should be tested to ensure that no air leaks are present.

If empyema develops more than 2 days after resection, the initial treatment includes administering broad-spectrum antibiotics, draining the space with close-tube drainage, and using flexible bronchoscopy to determine whether a bronchopleural fistula is present. If the patient is medically unstable, Eloesser flap should be performed to provide the best way to sterilize the space. If the patient is stable, treatment depends on whether bronchopleural fistula is present. If bronchopleural fistula is not present, a modified Clagett procedure, in which antibiotic solution is instilled and then drained to sterilize the fluid, can be performed.[61] However, if bronchopleural fistula is present, the treatment will vary based on the operative side, the size of the fistula, the availability of suitable muscle flaps, and a number of other factors. This discussion is beyond the scope of this chapter but muscle flap coverage of the fistula, and vascularized tissue placement to fill the postresectional, or even a thoracoplasty.

## FOLLOW-UP

All patients who complete chemo-, radio-, and/or surgical therapy for lung cancer should be followed with chest imaging for life. The NCCN guidelines recommend that imaging studies be performed every 4 to 6 months for the 2 years to detect potential recurrences and metastases and yearly thereafter to detect potential new primary tumors. After lung cancer resection, patients have a lifetime risk of 1 to 2 percent per year of developing a new primary tumor.[62]

## PROGNOSIS

### Small Cell Lung Cancer

The median overall survival for patients with limited disease small cell lung cancer is 12 to 20 months and 9 months for patients with extended disease.[63] A recent study of patients who underwent resection for small cell lung cancer found

that patients with stage I, II, or IIIA disease had overall 5-year survival rates of 56 percent, 40 percent, and 12 percent, respectively.[64]

## Nonsmall Cell Lung Cancer

The overall 5-year survival rates among NSCLC patients who underwent lung cancer resection at a major cancer center are 75 percent for stage IA disease, 68 percent for stage IB disease, 65 percent for stage IIA disease, 43 percent for stage IIB disease, and 37 percent for stage IIIA disease.[65] Patients with stage IIIB or IV disease have an overall 5-year survival rate of 3.5 percent.[11] NSCLC patients with bronchoalveolar and typical carcinoid tumors tend to have better prognoses than other NSCLC patients.

# CONCLUSIONS

Lung cancer is a leading cause of preventable death attributed to smoking and environmental exposure. It is the result of a series of genetic changes caused by environmental factors that allow cells to grow, proliferate, and metastasize. Most lung cancer patients present with late-stage disease. Patients' clinical symptoms depend on the location and size of the tumor and presence of metastasis. Lung cancer diagnosis is accomplished through the pathologic examination of a biopsied specimen of the mass. Clinical staging is based on a combination of patient history, physical exam, pathologic, and radiographic information. The patients with lung cancer patients are treated using multimodality therapy. Surgery and radiotherapy are used for local and regional disease; surgery remains the primary therapy, and radiotherapy is reserved for patients who cannot tolerate surgery. Chemotherapy is used to treat patients with regional and metastatic lung cancer. Overall, the prognosis for lung cancer is poor. The estimated overall 5-year survival rate for all of the patients with lung cancer is about 16 percent. The type and pathologic stage of the lung cancer is the best predictor for overall survival.

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## PRIMARY LUNG CANCER BOARD REVIEW QUESTIONS (CHAPTER 9)

1. Which is the most common growth pattern for adenocarcinoma of the lung?
   A. Central endobronchial tumor
   B. Background of pulmonary fibrosis
   C. Pseudomesotheliomatous carcinoma
   D. Diffuse pneumonia-like consolidation
   E. Peripheral tumor with overlying pleural retraction

2. Which of the following histology patterns is correct?
   A. Squamous: sheets of polygonal cells
   B. Atypical carcinoid: keratin pearls and intracellular bridges
   C. Large cell: two or fewer mitoses and no necrosis
   D. Small cell: ill-defined borders and absent nucleoli
   E. Typical carcinoid: multiple mitoses with necrosis

3. Which is not a risk factor for lung cancer?
   A. Xenon exposure
   B. Smoking
   C. Second-hand smoke
   D. Asbestos exposure
   E. Nickel exposure

4. Which staging is correct according to the 7th edition of the NSCLC staging system?
   A. T3 tumor, N2 disease = stage IIIB
   B. T1 tumor, N3 disease = stage IIIA
   C. T2a tumor measuring 4 cm = stage IB
   D. T2b tumor, N1 disease = stage IIA
   E. T4 tumor of vertebral body = stage IIB

5. Which of the following is true for lung cancer trials?
   A. The ACOSOG Z0030 trials showed no difference in survival between lymph node sampling and formal dissection.
   B. Diespierre et al. demonstrated a survival advantage for neoadjuvant chemotherapy in stage II cancer.
   C. The Adjuvant Lung Project Italy showed decreased survival in the chemotherapy group due to side effects from the aggressive regimen.
   D. The IALT demonstrated improvement in disease-free survival but not overall survival in the chemotherapy arm.
   E. The NCI of Canada study showed greatest survival benefit in stage IB patients.

## ANSWERS

1. **Answer: E.** The most common growth pattern of adenocarcinoma is a peripheral tumor that causes the overlying pleura to retract.
2. **Answer: D.** Small cell cancer is typified by ill-defined borders between cells and absent nucleoli. Sheets of polygonal cells are found in large cell cancers. Keratin pearls and intracellular bridges are found in squamous cell cancers. Typical carcinoids have two or fewer mitoses and no necrosis.
3. **Answer: A.** Radon, not xenon, exposure is associated with lung cancer.
4. **Answer: C.** A T2a tumor measuring between 3 and 5 cm is stage IB.
5. **Answer: A.** There was no difference in survival between lymph node sampling and formal lymph node dissection in the ACOSOG Z0030 trial.

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10

# Pulmonary Metastasis

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**KEY CONCEPTS**

- Metastatic disease to the lung is the second-most common pulmonary malignancy, affecting 20 to 54 percent of patients with cancer. A subset of patients with metastatic disease present with disease confined to the lung. Complete resection of this pulmonary burden of disease can result in 5-year survival rates as high as 40 to 50 percent.
- Pulmonary metastases are typically found on surveillance imaging. Very rarely are patients symptomatic with cough, pain, hemoptysis, or dyspnea.
- Helical, thin-sliced computed tomography is the gold standard for detecting pulmonary metastases. Pulmonary nodules as small as 3 mm can be detected with a sensitivity as high as 75 percent.
- Treatment options for secondary pulmonary malignancies include systemic chemotherapy, isolated lung perfusion or suffusion, radiofrequency ablation, stereotactic body radiation therapy, and surgical resection.
  - Isolated lung perfusion (ILuP) and suffusion are investigational and should be restricted to institutions with active research protocols.
  - The application of radiofrequency ablation (RFA) and stereotactic body radiation therapy (SBRT) is limited by the size and location of the nodule. These modalities are typically reserved for patients who are poor operative candidates or who refuse surgery.
  - Pulmonary metastasectomy is the treatment of choice for patients with metastatic colon cancer, renal cell carcinoma, sarcoma, melanoma, and nonseminomatous germ cell tumor. Surgery should also be considered for select patients with metastatic breast and head and neck cancer.
- Patients considered for pulmonary metastasectomy should meet the following criteria:
  - Primary site of disease is controlled or controllable.
  - Absence of extrathoracic metastases (or, in cases of oligometastases, extrathoracic sites of metastases are controlled or controllable).
  - The patient has the pulmonary reserve to tolerate the appropriate parenchymal loss for a complete resection.
  - Mediastinal and intrathoracic lymphadenectomy is advocated.
- Pulmonary metastasectomy is associated with the following survival rates:
  - Colorectal cancer 40 to 68 percent (5 years), renal cell carcinoma 47 to 74 percent (5 years), sarcoma 40 percent (5 years), melanoma 22 to 27 percent (5 years), and nonseminomatous germ cell tumor (NSCGT) 74 to 94 percent (5 years)
  - Pancreatic adenocarcinoma 40 percent (2 years), hepatocellular carcinoma 41 percent (5 years), breast carcinoma 35 to 80 percent (5 years), and head and neck squamous cell carcinoma 26 to 50 percent (5 years)
  - Disease-free interval, number of pulmonary metastases, and completeness of resection are significant predictors of long-term survival.

## INTRODUCTION

Pulmonary metastases are defined as secondary malignant tumors of the lung parenchyma or pleura. Originating from an entirely separate organ, metastatic disease to the lung is the second-most common pulmonary malignancy. Autopsy studies have demonstrated that 20 to 54 percent of patients who die with a diagnosis of cancer also have pulmonary metastases. A subset of these patients have metastases limited only to the lung. In their study of 162 sarcoma patients, Huth and Eilber reported that of the patients with recurrent disease, 88 percent had pulmonary metastases, with the lung being the sole site of disease in 72 percent.[1] Similarly, Billingsley and associates examined 230 patients with recurrent soft tissue sarcomas treated at Memorial Sloan–Kettering Cancer Center and found that 73 percent of these

patients had recurrences that appeared initially only in the lungs.[2] With a significant proportion of patients with metastatic malignancy confined to the lung, complete resection of the intrathoracic disease burden would render these patients disease-free.

Although the majority of operations for pulmonary metastasectomy can be performed via an open approach, thoracoscopic pulmonary metastasectomy has been demonstrated to be equally efficacious with similar survival rates and has the benefit of fewer adhesions, less pain, and shorter length of stay.

Weinlechner and colleagues published the first report of pulmonary metastasectomy in 1882.[3] In 1927, Tudor Edwards performed a sublobar resection for recurrent sarcoma following an amputation 6 years earlier. Barney and Churchill described a lobectomy after nephrectomy for synchronous metastatic kidney cancer in 1933; the patient subsequently survived for 23 years.[4] Blalock described the first pneumonectomy for metastatic large bowel carcinoma at a "recent advances" lecture in 1944.[5]

In 1947, Alexander and Haight published a case series of pulmonary metastasectomies, proposing the first set of selection criteria for surgery.[6] Since then, pulmonary metastasectomy has become a widely accepted treatment modality for patients with metastatic disease. Recent series have described 5-year survival rates of 40 percent in osteogenic sarcoma,[7] 38 percent in soft tissue sarcoma,[8] 40 percent in colorectal carcinoma,[9] and 50 percent in patients with breast carcinoma.[10]

## PATHOPHYSIOLOGY

Stephen Paget first described his "seed and soil" hypothesis in 1889. He observed that metastatic disease fell in a nonrandom pattern and postulated an affinity of certain primary cancer types (the "seed") toward factors within the metastatic target organ (the "soil"). In 1928, James Ewing challenged this hypothesis, proposing that metastasis was directly related to the anatomy of the vascular system instead. Regardless of which of these two hypotheses holds true, new improvements in cellular, molecular, and imaging techniques have elucidated that the development of metastatic lesions is the result of a complex, multistep process known as the metastatic cascade.[11] In order for a metastatic focus of cancer cells to form, cells from a growing tumor need to escape the local environment (intravasation, resistance to anoikis), travel while avoiding host defenses (evasion of the immune system), leave the bloodstream (extravasation), and begin the process of implantation and growth (dormancy and proliferation).

Recent advances in identifying the gene expression profiles of varying tissues have led to investigations in identifying a signature of genes characteristic of metastatic tumors. Gene expression profiling studies using cDNA microarrays comparing the expression profiles of primary tumors with the expression profiles of metastatic tumors in patients with breast cancer have identified a 70-gene signature that successfully differentiated tumors with poor versus good prognosis.[12] Ramaswamy and coworkers identified a metastatic signature based on gene expression profiling that could predict the presence of metastases across a variety of adenocarcinomas.[13] Lastly, although similar studies in humans are yet to be performed, Minn and colleagues were able to identify an expression signature characteristic of pulmonary metastases in a murine model.[14] Undoubtedly, understanding the metastatic cascade and elucidating the mechanisms of each step will provide insight into potential treatments against metastatic disease.

## CLINICAL FEATURES

Secondary tumors of the lung are most often an occult finding during surveillance imaging after primary tumor resection. Patients are typically asymptomatic. Rarely, patients with pulmonary metastases will present with symptoms of dyspnea, cough, hemoptysis, or pain. Pleural involvement may result in pneumothorax or pain. Thorough history taking may elicit a history of unintentional weight loss, general malaise, or decreased energy. Physical examination is likely to be negative for significant findings.

## DIAGNOSTIC MODALITIES

Although plain chest radiography was previously the mainstay of screening for pulmonary metastases, computed tomography (CT) has emerged as the most commonly used screening imaging modality and is the current standard. On CT imaging, pulmonary metastases appear as single or multiple pulmonary nodules within the lung parenchyma. In general, these lesions are rounded and well circumscribed. Hilar or mediastinal lymphadenopathy may also indicate lymphatic involvement. In some cases, the pulmonary nodule(s) may contain tissue elements consistent with the primary site (e.g., calcification in metastatic osteosarcoma or fatty elements in liposarcoma).

High-resolution CT (HRCT) can detect pulmonary nodules as small as 3 mm. In a study comparing conventional CT with HRCT, Margaritora and colleagues reported a sensitivity of 100 percent for both types of scans for nodules 10 mm in size.[15] The sensitivity of nodules smaller than 6 mm dropped to 62 and 48 percent with conventional CT and HRCT, respectively. Overall sensitivity for pulmonary metastases was 82.1 percent. In examining the sensitivity of thin-slice CT, Pfannschmidt and coworkers found the overall sensitivity of 3- and 5-mm slices to be 88.8 and 83.7 percent, respectively.[16] The sensitivity decreased to 74.7 (3-mm slices) and 64.0 percent (5-mm slices) for nodules smaller than 5 mm.

The use of positron emission tomography (PET) scan in the detection of pulmonary metastasis has also been studied. Fortes and colleagues found an overall sensitivity of 67.5 percent in the detection of pulmonary metastases with

PET imaging.[17] For lesions 10 mm or greater in size, the sensitivity of PET was 87.8 percent; however, for lesions smaller than 10 mm, sensitivity was only 29.6 percent. It is also notable that the sensitivity varied with histology. For metastases with squamous cell carcinoma histology, sensitivity of the exam was 93 percent. For sarcoma, the sensitivity of PET was 44 percent. Although the sensitivity of PET imaging is variable and this modality should not be used solely for the screening of pulmonary metastases, it does serve as an adjunct to CT imaging and is particularly useful in evaluating for the presence of extrathoracic disease.

## MEDICAL THERAPY

### Chemotherapy

Systemic chemotherapy should be used for patients with widely metastatic disease or as an adjunct to surgical therapy in patients with metastatic germ cell tumor or breast cancer. Patients with a solitary pulmonary metastasis or oligopulmonary metastases should be considered for surgical resection, as 5-year survival following resection can be as high as 40 percent.[18] Patients who cannot tolerate surgery or refuse surgery for metastases confined to the lung should be considered for other forms of locoregional therapy such as radiofrequency ablation (RFA), stereotactic body radiation therapy (SBRT), or isolated lung perfusion (ILuP).

### Radiofrequency Ablation

RFA uses an alternating current to create frictional heating of tissue, resulting in tissue necrosis. A radio wave—emitting electrode is inserted into the tumor, which is then heated to 90°C to 100°C to produce coagulation necrosis. Originally used in the treatment of hepatic tumors, the use of RFA was soon extended to the treatment of pulmonary malignancies. Candidates for RFA should have disease confined to the lung(s) or otherwise controlled. In addition, lesions amenable to RFA should be small in diameter (less than 3 cm in diameter) and should not abut mediastinal structures, which may act as a heat sink.[19]

In general, RFA is associated with low morbidity and mortality. Common complications associated with RFA are usually mild and self-limited. Patients should be counseled regarding the possibility of pain during the procedure, pneumothorax (possibly requiring thoracostomy tube management), fever, hemoptysis, cough, pleural effusion, hemothorax, and abscess formation in the ablation bed.

Lesion size is an important consideration of RFA for treatment of metastatic disease. Several authors have demonstrated statistically significant differences in response rates as well as overall survival for lesions greater than 3 cm versus those smaller than 3 cm.[20,21] In a study of RFA for renal cell carcinoma metastases, the 5-year survival of patients with fewer than six nodules that were less than 6 cm in diameter was 100 percent. Recurrence-free survival was 92 percent at 1 year and 23 percent at 5 years. Another study of 22 patients with metastases of varying histology demonstrated a 2-year survival of 68 percent. Lesion size was found to be a significant prognostic factor in both recurrence and survival.[19]

One important aspect to remember regarding RFA is that since there is no pathologic analysis, the treatment margin is unknown. A study of RFA of 18 pulmonary lesions that were subsequently resected for pathologic analysis demonstrated only 39 percent of lesions were completely ablated and only 50 percent of patients had more than 90 percent tumor ablation.[22] More importantly, 11 percent of patients had less than 90 percent tumor ablation. Although the authors contend that early pathologic analysis may have underestimated the effectiveness of tumor ablation, these results are inferior to those achieved with surgical resection. Therefore, RFA should be reserved for treating pulmonary metastasis in patients who are medically inoperable or who refuse surgery.

### Stereotactic Body Radiation Therapy

SBRT is a technique that uses precisely targeted radiation. This technique facilitates the delivery of higher doses of radiation to the target anatomy, resulting in better tumor control, while minimizing harmful effects to adjacent normal tissue. Patients being considered for SBRT should meet the same criteria as those being considered for RFA. Although data regarding SBRT for pulmonary metastases are limited, a multi-institutional Phase I/II trial of SBRT for pulmonary metastases demonstrated local control of 100 and 96 percent at 1 year and 2 years, respectively, and a median survival of 19 months.[23]

Compared with conventional radiotherapy, SBRT has several unique features. First, the doses of radiation administered are high and localized. To reduce treatment toxicity, there are tight dose distributions around the tumor, with rapid dose falloff in the surrounding lung parenchyma. During planning and treatment, the radiation oncologist can account for tumor motion. Finally, there is a reproducible patient immobilization to minimize movement during treatment sessions. Complications associated with SBRT affect up to 5 percent of patients, and most commonly are pneumonitis (grade 2 and higher) and rib fractures.

A significant limitation to SBRT is that the treated lesions should be small in diameter. In addition, the treatment of multiple lesions presents as a challenge while attempting to minimize toxicity to adjacent, normal lung parenchyma. As such, although SBRT should not be the primary modality used in treating secondary pulmonary malignancies, it can serve as a good alternative in treating poor surgical candidates or as an adjunct to surgical therapy in patients with multiple lesions.

## SURGICAL THERAPY

### Surgical Metastasectomy

Surgical resection is the mainstay of therapy for patients with secondary pulmonary malignancies in the absence of extrapulmonary disease and controlled primary disease. Alexander and Haight proposed the first set of selection criteria, listed in Table 10-1, for patients eligible for pulmonary metastasectomy.[6] First and foremost, the site of primary disease must be either controlled or controllable. Ideally, the patients should also have an absence of extrapulmonary disease. For patients with an additional site of metastatic disease outside the lung, the extrapulmonary disease should be controlled or controllable. Finally, the patient should have sufficient pulmonary reserve to tolerate the loss of lung parenchyma required to achieve a complete resection. With the appropriate selection of patients, 5-year survival rates of 20 to 40 percent have been reported.[18]

Patients who are candidates for resection may be treated with either open approach or thoracoscopic approach. Proponents of open resection state that open surgery is mandatory for sufficient manual palpation of the lung parenchyma. However, supporters of thoracoscopic surgery assert that the sensitivity of HRCT obviates the need for manual palpation and that the benefits of a thoracoscopic approach outweigh those of an open approach. Compared with thoracotomy, benefits of thoracoscopy include decreased postoperative pain, decreased chest tube duration, decreased hospital length of stay, faster recovery, and decreased inflammatory response facilitating re-do surgery.

In an attempt to provide guidelines for surgical approach in pulmonary metastasectomy, the European Society of Thoracic Surgeons working group carefully evaluated the considerations involved in decision-making.[24] They narrowed the issue of surgical approach to four questions: (1) What is the evidence for the need for palpation of the lung in the modern era of imaging? (2) Is there evidence of a difference in outcome for an open versus a closed approach? (3) Is there evidence for a difference in outcome for an initial policy of bilateral versus unilateral exploration? (4) In patients with known bilateral disease, is there a difference in outcome with simultaneous versus a staged approach? Each of these topics is an important consideration in the surgical approach to pulmonary metastases.

**TABLE 10-1: Criteria for Surgical Resection of Pulmonary Metastasis**

**Alexander and Haight criteria for resection of secondary pulmonary malignancy**

- Primary tumor is controlled (or is controllable)
- Any extrapulmonary disease is controlled (or is controllable)
- Patient must be fit for surgical resection (patient's pulmonary reserve will tolerate pulmonary resection)

As previously mentioned, HRCT has an overall sensitivity of 88.8 and 83.7 percent for 3 and 5 mm slices, respectively.[16] Although the sensitivity decreased to 74.7 (3-mm slices) and 64.0 percent (5-mm slices) for nodules less than 5 mm in size, it is difficult to argue that manual palpation has a sensitivity superior to HRCT scans currently available. However, in early studies investigating the need for manual palpation of metastatic disease, 10 of 15 patients had additional nodules that were not identified on CT scans or during their video-assisted thoracic surgery (VATS) procedures.[25] More recent studies have similarly reported the identification of additional nodules during thoracotomy that were not recognized either on CT imaging or during thoracoscopy.[26–28]

Although an open approach may identify more nodules than during thoracoscopy, this finding does not translate to improved survival. In a review of seven studies by Molnar, six demonstrated no difference in survival between patients undergoing metastasectomy by VATS versus open surgery.[24] Moreover, patients undergoing thoracotomy experience significantly more complications than those who have similar parenchymal resection by thoracoscopy.[28] In a recent cohort study comparing patients treated with metastasectomy via VATS versus thoracotomy, Carballo and associates demonstrated a 5-year overall survival of 58.8 percent for thoracotomy and 69.6 percent for VATS ($p = 0.03$).[29] There were no statistically significant differences between the two groups in terms of recurrence-free survival.

Finally, there are no data demonstrating a difference in outcome between an initial policy of bilateral versus unilateral exploration and simultaneous versus staged approach in patients with known bilateral disease. Results from the European Society of Thoracic Surgeons working group survey suggested that an initial approach via median sternotomy is reasonable for patients with known bilateral disease.[24] In cases not suitable for median sternotomy, such as posterior lesions or patients with previous pulmonary resection, staged thoracotomy with a 3- to 6-week interval was recommended. Zheng and colleagues recommended a similar approach to pulmonary metastasectomy except that these authors were more supportive of a thoracoscopic approach.[19]

In our experience, complete thoracoscopic resection of pulmonary metastases is possible in 75 percent of cases. We have resected as many as six ipsilateral nodules in a single setting, and have routinely had success in resecting nodules less than 5 mm in diameter. Figure 10-1 depicts an algorithm for managing pulmonary metastasectomy.

Ultimately, the main tenet of surgical resection of pulmonary metastases is complete resection. Peripheral nodules should be treated with wedge resection; more central nodules may require a segmentectomy, lobectomy, or, rarely, pneumonectomy. With regard to open versus thoracoscopy, "there is such evident variation that depends on the particular needs of the patient and the preference of the surgeon that it might well be a situation in which it is a decision for individual craftsmen to do what works best in their hands."[24]

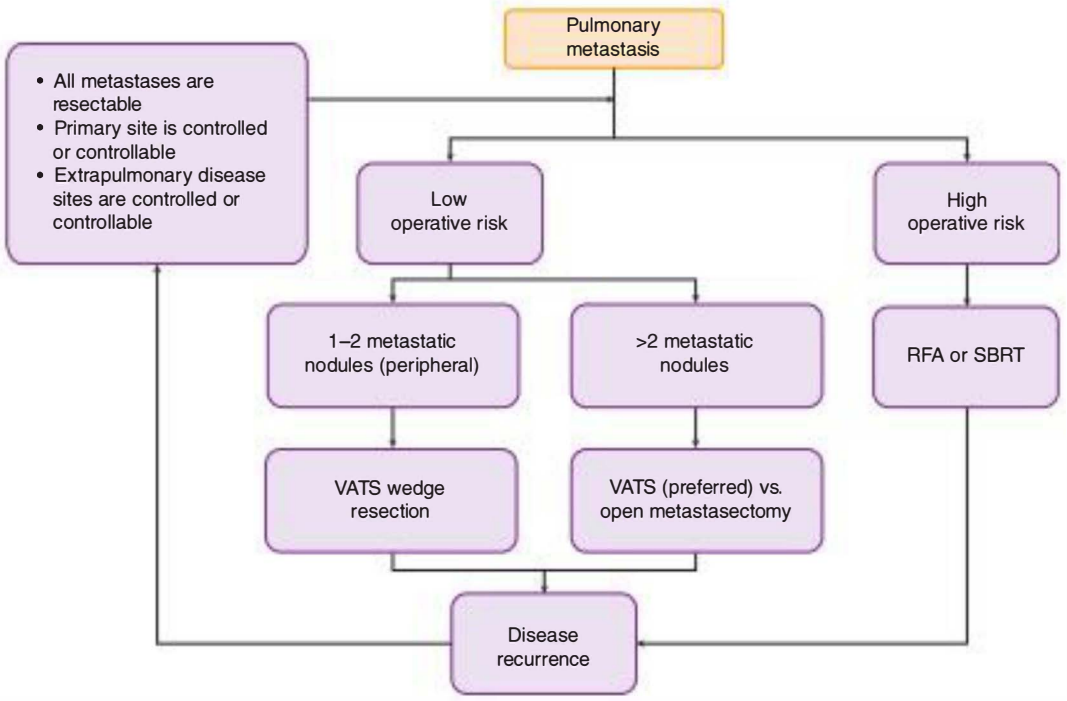



**FIGURE 10-1** Suggested treatment algorithm for management of pulmonary metastases. Patients with pulmonary metastases must first meet the criteria for resection (controlled primary disease, absence of extrathoracic metastases, ability to tolerate resection of lung parenchyma). Patients who are operative candidates with adequate pulmonary reserve should undergo thoracoscopic (preferred) versus open resection. Patients who are at high risk for perioperative morbidity and mortality should be considered for radiofrequency ablation (RFA) or stereotactic body radiation therapy (SBRT). Patients who have recurrent disease should be reevaluated for surgical resection. (From Zheng F, Fernando H (eds). *Surgical and Nonresectional Therapies for Pulmonary Metastasis*. 2010; 90(5):1041–1051. With permission from Elsevier.)

As for any lung resection, preoperative planning should include pulmonary function testing and an evaluation of the patient's ability to tolerate an operation. Patients receiving certain chemotherapeutic agents are at risk for drug-induced lung disease, including interstitial pneumonitis and fibrosis, hypersensitivity pneumonitis, and acute pneumonia. Specific agents implicated in these disorders include bleomycin, mitomycin C, busulfan, cyclophosphamide, carmustine, gefitinib, paclitaxel, and methotrexate. It is mandatory for the surgeon to communicate with the anesthesiologist prior to surgery regarding the patient's prior exposure to chemotherapeutic agents and to attempt to minimize the fractional inspired oxygen ($Fio_2$) to avoid oxygen toxicity. Finally, patients are required to engage in smoking cessation for at least 3 weeks prior to surgery to reduce the risk of postoperative pneumonia and other complications.

## Extended Pulmonary Resection for Metastatic Disease

A small minority (less than 3%) of patients with metastatic disease will require extended resection, defined as pneumonectomy or other lung resection with en bloc resection of chest wall, pericardium, superior vena cava, or other thoracic structures. For these patients, very rigorous consideration of strict preoperative selection criteria, including the probability of complete resection, should be undertaken. Cardiopulmonary bypass may be used in rare instances when tumors involve or invade the great vessels or cardiac structures, and operation is considered for either cure or palliation of symptoms.

Several series of extended resections for metastatic disease have been reported in the literature, with good results. Spaggiari and associates reported a 5-year survival of 16 percent in a series of 42 patients who underwent pneumonectomy for metastatic disease from various primary sites.[30] Similarly, Putnam and colleagues demonstrated a 5-year actuarial survival of 25.4 percent in 38 patients undergoing extended resection, 19 of which had pneumonectomy. Overall mortality was 5.3 percent and occurred in patients undergoing pneumonectomy.

In a review of the International Registry of Lung Metastases, Koong and coworkers reported that 133/5206 (3%) patients underwent primary pneumonectomy for metastatic disease and 38/5206 (1%) underwent completion pneumonectomy.[31] Patients who had complete resection had a 5-year survival rate of 20 percent. Those whose disease

could not be completely resected had a perioperative mortality of 19 percent with a poor 2-year survival rate. Favorable prognostic factors for patients undergoing pneumonectomy for pulmonary metastasis include complete resection, single metastasis, and negative mediastinal lymph node status.

## Recurrent Pulmonary Metastases

In some instances, reoperation is indicated for management of recurrent pulmonary metastases. Patients being considered for reoperation should be selected by the same criteria as for primary operation for pulmonary metastases. That is, the primary and/or other extrathoracic disease site(s) must be controlled and the patient must be physiologically able to tolerate surgery and lung resection.

Most series describing reoperation for pulmonary metastases are small, and consist of patients with primary sarcoma. Median survival for patients with resectable disease ranges from 14.5 to 70 months, depending on the tumor histology.[32,33] The reported 5-year survival after reoperation for sarcomatous lung metastases is 22 percent. Two or fewer nodules, size less than 2 cm, and low-grade primary tumor histology are favorable prognostic factors.

## Lymphadenectomy as an Adjunct to Metastasectomy

The question of whether or not to perform a complete mediastinal lymph node dissection in the setting of pulmonary metastasectomy remains a debate. Most studies evaluating pulmonary metastasectomy have inconsistently included either lymph node sampling or lymph node dissection. As a result, the majority of current reported incidences of lymph node involvement are likely underestimates.

Data from the International Registry of Lung Metastases reported metastasis to hilar or mediastinal lymph nodes in 5 percent of patients.[18] Specific to disease, 11 percent of germ cell tumors, 8 percent of melanomas, 6 percent of epithelial tumors, and 2 percent of sarcomas harbored lymph node metastases. However, more recent studies that included systematic lymph node dissections have reported lymph node involvement in up to 32 percent cases, including a study on patients with metastatic sarcoma, of whom 19 percent had lymph node involvement.[34]

The involvement of regional, hilar, or mediastinal lymph nodes is an important prognostic factor. In a series of 245 patients with lung metastases of various primary sites, Pfannschmidt reported a median survival of 63.9 months in patients without lymph node involvement (N0 disease), compared with 32.7 months and 20.6 months for patients with N1 disease and N1 + N2 disease, respectively.[35] Similarly, Welter and associates reported a 5-year survival of 78.5, 0, and 0 percent in patients with colorectal cancer and pulmonary, hilar, and mediastinal lymph node metastases, respectively.[36] As such, a formal and systematic evaluation of hilar and mediastinal lymph nodes should routinely be performed during pulmonary metastasectomy.

## Isolated Lung Perfusion

ILuP allows the selective delivery of a chemotherapeutic agent into the lung while diverting the venous effluent. With this technique, higher and more toxic doses of chemotherapy can be delivered with fewer adverse effects as compared with intravenous chemotherapy. Drug metabolism by the liver or kidneys to inactive forms is avoided, as are high drug levels in critical organs.

Unilateral ILuP is performed by first cannulating the pulmonary artery and pulmonary veins. These cannulas are then connected to an extracorporeal circuit. The vessels are clamped centrally, and the chemotherapeutic agent is injected into the circuit. Perfusion of both lungs simultaneously requires two extracorporeal systems to completely separate the systemic and pulmonary circulation.

Although several animal studies on ILuP demonstrated promising results, studies in humans thus far have been limited to Phase I/II clinical trials with mixed results. In a thorough review of ILuP, Van Schil et al. described seven studies using various chemotherapeutic agents on metastatic sarcoma, melanoma, Ewing sarcoma, renal cell carcinoma, adenoid cystic carcinoma, and colon carcinoma.[37] Out of 32 patients with metastatic sarcoma treated with doxorubicin, only 1 had a major response, 1 patient had stabilization of disease on the treated side (with progression of disease on the untreated side), and the remainder of the patients had neither a partial nor a complete response. Complications included pneumonia ($n = 2$), lung injury ($n = 1$), paradoxical tumor embolus ($n = 1$), and sternal nonunion ($n = 1$). Two of the three studies using doxorubicin identified a significant decrease in pulmonary function ($FEV_1$, FVC, or DLCO) following treatment. A decrease in pulmonary function was also noted in six patients with metastatic sarcoma who were treated with cisplatin. Of 10 patients treated with cisplatin, 6 developed pulmonary edema, one of whom required prolonged mechanical ventilation. Three patients were disease-free at 12 months, and one patient was disease-free in the chest but succumbed to cerebral metastases at 13 months. In a study using TNF-α as the chemotherapeutic agent, only 3 of 16 patients treated demonstrated short-term partial response and ultimately had progression of disease 6 to 9 months following therapy. Lastly, of 23 patients treated with melphalan, 8 were disease-free at 25 months while 14 patients had recurrent disease.

To date, studies on ILuP are limited to Phase I/II trials and the studied involved a variety of chemotherapeutic agents and target histology. As such, it is difficult to interpret the results and make any generalizations on the application of ILuP. Although experimental data support the use of ILuP, these techniques remain experimental and their use should be restricted to centers with special interests in regional therapy for lung metastases.

### Isolated Lung Suffusion

Similar to ILuP, lung suffusion involves the injection of a chemotherapeutic agent into a pulmonary artery. The artery is clamped proximal to the injection site. In contrast to ILuP, however, lung suffusion involves isolation and clamping of the pulmonary veins. This allows for uniform distribution of the chemotherapy through the entire lung, with slow leakage into the systemic circulation. Lung suffusion can be achieved using minimally invasive techniques. To date, the use of lung suffusion in humans has been restricted to Phase I clinical studies.

## OUTCOMES AND PROGNOSIS

Although resection of secondary pulmonary malignancies had been performed for many decades, data in support of this practice were lacking. Therefore, in 1991, the International Registry of Lung Metastases was established to establish the long-term results of pulmonary metastasectomy. The results of this effort, an analysis of 5206 cases of epithelial cell, sarcoma, germ cell, and melanoma metastasectomies, were published in 1997.[18] In this study, actuarial 5-, 10-, and 15-year survival was 36, 26, and 22 percent (median 35 months), respectively, for patients who underwent complete resection of metastases. In contrast, those who had incomplete resections had an actuarial survival of 13 percent at 5 years and 7 percent at 10 years (median 15 months). In addition, 5-year survival was significantly greater for patients with a longer disease-free interval (DFI; 45% for DFI longer than 36 months vs. 33% for DFI up to 11 months) and a single focus of metastasis (43% for single lesion vs. 27% for >4 lesions). Multivariable analysis demonstrated a more favorable prognosis based on histology, with germ cell tumor being the best and melanoma being the worst. These findings were further supported in a more recent single-institution study of 708 pulmonary metastasectomies.[38]

### Colorectal Carcinoma and Other Gastrointestinal Epithelial Cell Carcinomas

Secondary pulmonary malignancies of epithelial cell origin are the most common metastatic pulmonary disease. Of these malignancies, thoracic surgeons most frequently encounter pulmonary metastases from a colorectal primary malignancy. Resection of these pulmonary metastases has become a common practice. Surgical resection is associated with low morbidity and mortality as well as long-term survival rates up to 40 to 68 percent in a select population of patients.[39] In a review of 378 patients undergoing pulmonary metastasectomy of colorectal malignancies at Duke University and Memorial Sloan–Kettering Cancer Center, 3-year overall survival was 78 percent and 3-year disease-free survival (DFS) was 28 percent.[40] Independent predictors of recurrence were a DFI of less than 1 year and more than three pulmonary lesions at the time of presentation.

For colorectal carcinoma, there are conflicting data regarding whether a history of a previously resected hepatic metastasis is of prognostic value. Zabaleta and colleagues concluded that a prior history of a hepatic metastasis predicted a poorer prognosis while Jarabo and associates reported otherwise.[41,42] In both studies, however, multivariable analysis identified the presence of metastatic disease in mediastinal or pulmonary lymph nodes as a predictor of poorer prognosis. In addition, prognosis did not decrease with repeated pulmonary resection. No randomized trials investigating the validity of surgical resection of colorectal pulmonary metastases exist. To this end, the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) trial is currently underway.[43]

Data regarding pulmonary metastasectomy of other gastrointestinal epithelial cell cancers are fewer and limited to case series and anecdotal information. In a study of 31 Stage I/II pancreatic adenocarcinoma patients, Arnaoutakis and coworkers reported no morbidity or mortality following pulmonary metastasectomy, an increase in median cumulative survival (51 months vs. 23 months; $p < 0.04$), and a trend toward improved overall 2-year survival (40% vs. 27%; $p = 0.02$).[44] For metastatic hepatocellular carcinoma, Kitano et al. reported a 5-year survival of 40.9 percent and a 2-year DFS of 19.5 percent in 45 patients.[45]

### Renal Cell Carcinoma

Data regarding pulmonary metastasectomy for renal cell carcinoma typically are included in large studies on pulmonary metastasectomy, without focusing on outcomes specific to renal cell carcinoma.[18,38] However, in a large series of 191 patients, Pfannschmidt and colleagues reported that the length of the DFI, the number of pulmonary metastases, and the involvement of lymph node metastases were all independent predictors of survival following metastasectomy for renal cell carcinoma.[46] Overall 5-year survival was 42.1 percent in patients without lymph node metastasis and who underwent complete resection. Similarly, Alt et al. from the Mayo Clinic reported a 5-year cancer-related survival rate of 73.6 percent with complete resection in 49 patients with metastases confined to the lung.[47] Moreover, they supported resection in the setting of multiple-site renal cell carcinoma metastases, demonstrating prolongation of median cancer-related survival in patients who underwent complete resection (4.8 years complete resection vs. 1.3 years incomplete resection; $p < 0.001$).

Kanzaki and associates reported long-term outcomes in a single-institution 25-year experience on pulmonary metastasectomy for renal cell carcinoma.[48] Of 48 patients who underwent 59 resections (8 of whom had additional resections for pulmonary recurrence), the 3-, 5-, and 10-year overall survival rates were 60, 47, and 18 percent, respectively. On multivariate analysis, DFI greater than 2 years and complete resection were identified as positive prognostic factors.

## Osteogenic Sarcoma

When considering pulmonary metastasectomy, one must distinguish soft tissue sarcoma from osteogenic sarcoma. Osteogenic sarcoma may develop pulmonary metastases in up to 80 percent of patients after initial treatment.[1] Because the lung is often the only site of metastatic disease in patients with osteogenic sarcoma, pulmonary metastasectomy may render these patients disease free. Both Snyder and Putnam, in their series of 21 and 39 patients, respectively, reported 5-year survival rates of nearly 40 percent in patients with osteogenic sarcoma who underwent pulmonary metastasectomy.[7,49] The presence of three or fewer nodules on preoperative imaging, longer DFI, and the presence of resectable metastases were associated with longer postthoracotomy survival. Conversely, lack of primary tumor control, incomplete excision of metastases, and disease progression during treatment have all been shown to be negative prognostic indicators.[50]

## Soft Tissue Sarcoma

Soft tissue sarcomas are nonossifying tumors arising from connective tissue elements. Approximately 23 percent of patients with soft tissue sarcoma will develop distant metastases.[2] As with osteogenic sarcoma, the majority of distant recurrences present initially within the lungs; median survival after the development of lung metastases is approximately 1 year.

Pulmonary metastasectomy may be useful in selected patients with metastatic soft tissue sarcoma. In a large series of 255 patients, Van Geel and colleagues reported a 5-year survival of 38 percent for patients with soft tissue sarcoma undergoing pulmonary metastasectomy.[8] In a more recent study, Sardenberg reported a 7.5-year survival rate of 34.7 percent.[51] As with other primary sites, a longer DFI (greater than 6 months) and fewer than three nodules are associated with a higher overall 5-year survival.

The role of adjuvant chemotherapy following resection is unclear and currently under investigation. What is clear, however, is that some patients benefit from repeat resection. In several series of patients with recurrent pulmonary metastases from soft tissue sarcoma, patients whose tumors were completely resected in repeat surgical procedures had significantly longer overall survival compared with those whose tumors were either incompletely resectable or unresectable.[32,52]

## Melanoma

Thirty percent of patients with previously treated melanoma will develop metastatic disease, and approximately 40 percent of these patients will have isolated pulmonary metastases. Patients with Stage IV melanoma have a median survival of 6 to 8 months and a 5-year survival of less than 5 percent. In their review of pulmonary metastasectomy for melanoma, Oliaro and coworkers reported 5-year survival rates of 22 to 27 percent, which is consistent with other published results.[53] Petersen and colleagues estimated 13, 17, and 23 percent risk of developing pulmonary metastases at 5, 10, and 20 years, respectively, in a large longitudinal database of melanoma patients.[54] Multivariable analysis demonstrated that nodular histologic type, DFI shorter than 1 year, more than two pulmonary metastases, and the presence of extrathoracic metastases were predictors of poor prognosis. Conversely, completion of pulmonary metastasectomy was identified as an independent predictor of improved prognosis and associated with a survival advantage. There was no significant difference in survival between patients undergoing single metastasectomy and those undergoing repeated pulmonary metastasectomy (median survival 17 vs. 15 months; $p = 0.9$). As such, pulmonary metastasectomy should be considered for patients with Stage IV melanoma who have fully controlled primary disease, a limited number (2 or fewer) of pulmonary metastases, absence of extrathoracic disease on PET or CT imaging, and a long DFI between the diagnosis of the primary and metastatic disease.

## Breast Carcinoma

Although the minority of patients with metastatic breast cancer has disease confined to the lung, there is evidence of benefit to pulmonary metastasectomy in selected patients. In a recent review of the International Registry of Lung Metastases, Friedel and colleagues examined outcomes of 467 patients who underwent lung resection for metastatic breast cancer.[55] In this series, 5-, 10-, and 15-year survival rates were 38 percent, 22 percent, and 20 percent, respectively. Other studies on pulmonary metastasectomy in patients with breast cancer have reported similar survival, with 5- and 10-year survival rates as high as 35 to 80 percent and 8 to 60 percent, respectively.[56] DFI greater than 36 months, complete resection, and solitary metastasis were associated with improved outcomes.

## Squamous Cell Carcinoma of the Head and Neck

Experience with pulmonary metastasectomy for malignancies of the head and neck is limited, and most reports describe experience with small case series. However, the data suggest that pulmonary metastasectomy for patients with head and neck squamous cell carcinoma may result in good long-term outcomes. In a study of 25 patients undergoing pulmonary metastasectomy, Haro and colleagues reported 3- and 5-year survival rates of 53.3 and 50 percent, respectively.[57] The largest case series in the literature, a retrospective review of 237 patients by the Metastatic Lung Tumor Study Group of Japan, reported a lower 5-year survival of 26.5 percent.[58] Favorable prognostic factors include the presence of a solitary metastasis, early stage of head and neck primary, complete resection, and longer DFI.

Many authors have written that pulmonary metastases from squamous cell carcinoma originating in the oral cavity

and oropharynx portend a worse prognosis. For example, Mochizuki and associates found that 21 of 23 patients with an oral tongue primary undergoing pulmonary metastasectomy died of their malignancy within 2 years of metastasectomy.[59] They concluded that even for patients with solitary pulmonary metastasis of oral tongue cancer, surgical metastasectomy is not a recommended treatment option. Other predictors of poor prognosis include age greater than 60 years, male sex, lymph node metastasis, and incomplete resection.

## Nonseminomatous Germ Cell Tumor

Approximately 8 percent of patients with clinical Stage I nonseminomatous germ cell tumor (NSCGT) will develop pulmonary metastases. For patients with NSCGT, resection of residual masses in either the lung or mediastinum after chemotherapy is indicated. Large published series have reported excellent long-term outcomes with low morbidity and mortality. A review of the literature by Pfannschmidt reported an overall 5-year survival between 74 and 94 percent following complete resection of pulmonary and/or mediastinal metastases.[60] Complete resection was achievable in 78.5 to 87 percent of the cases. The number of metastases is of prognostic significance, as is the presence of viable malignant cells in the completely resected masses.[61] Older age at the time of diagnosis and the presence of nongerm cell cancer in testicular specimens are favorable prognostic indicators.[62]

## Gynecologic Tumors

The lung is an uncommon site of metastasis for uterine and cervical carcinoma. However, pulmonary metastasectomy has been described in several series. Depending on the histologic type, 5-year survival may range from 37.9 (leiomyosarcoma) to 86.5 percent (choriocarcinoma).[63] As with other primary sites, a longer DFI and complete resection are favorable prognostic factors. Conversely, primary cervical tumor has been shown to be a negative prognostic factor.[64]

# SUMMARY

Up to 54 percent of patients with cancer may develop pulmonary metastases. In many of these cases the lung is the single focus of metastatic disease. For these patients, pulmonary metastasectomy should be considered and can result in 5-year survival rates as high as 40 to 50 percent. For most primary tumors, a longer DFI, complete resection, and solitary site of metastasis are favorable prognostic factors. The surgeon should aim to achieve complete resection while sparing as much lung parenchyma whenever possible. Although median sternotomy and thoracotomy may be used as surgical approaches, a thoracoscopic approach is more efficient with regard to postoperative pain, chest tube duration, and hospital length of stay, with comparable long-term survival outcomes. Only rarely is an extended resection indicated for management of pulmonary metastases. For patients who refuse or are unable to tolerate surgery, RFA or stereotactic body radiotherapy should be considered.

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## PULMONARY METASTASIS BOARD REVIEW QUESTIONS (CHAPTER 10)

1. Which of the following is not a criterion for pulmonary metastasectomy?
   A. Primary malignancy is controlled
   B. Fewer than three pulmonary nodules
   C. Absence of extrathoracic metastases
   D. Sufficient pulmonary reserve to tolerate proposed resection

2. Which of the following is the most important factor during resection of pulmonary metastases?
   A. Number of metastases
   B. Disease-free interval
   C. Tumor doubling time
   D. Completeness of resection

3. Which of the following patients is the best candidate for immediate pulmonary metastasectomy?
   A. A 79-year-old patient with COPD and bilateral pulmonary nodules identified 2 months following radiation therapy for oral tongue cancer.
   B. A 56-year-old female with a history of breast cancer 5 years ago with a PET positive left internal mammary node and a peripheral single pulmonary nodule in the right upper lobe.
   C. A 25-year-old male 3 years after systemic therapy of nonseminomatous germ cell tumor with two ipsilateral pulmonary nodules and elevated serum markers.
   D. A 50-year-old male with a history of Stage II colon cancer 4 years ago and two pulmonary nodules, one in either hemithorax.

4. Which of the following is not a treatment option for a patient with pulmonary metastases and poor pulmonary function?
   A. Isolated lung perfusion
   B. Systemic chemotherapy
   C. Radiofrequency ablation
   D. Stereotactic body radiation therapy

5. The gold standard for imaging pulmonary metastases is
   A. Plain chest radiography
   B. Computed tomography
   C. Positron emission tomography
   D. Combined computed/positron emission tomography

## ANSWERS

1. **Answer: B.** Criteria for surgical resection of pulmonary metastases are that both the primary malignancy and any extrathoracic metastases (if present) are controlled or controllable. Ideally, there would be an absence of extrathoracic disease. Lastly, the patient must be able to tolerate the proposed surgery. The number of pulmonary metastases is not a factor in the selection of patients as long as a complete resection is achievable.
2. **Answer: D.** Completeness of resection is the single most important predictor of outcome following pulmonary metastasectomy. Long disease-free interval and slow tumor doubling time are also predictors of improved prognosis, but number of metastases is an inconsistent predictor of survival.
3. **Answer: D.** Criteria for pulmonary metastasectomy are that both the primary malignancy and any extrathoracic metastases (if present) are controlled or controllable. The patient must be able to tolerate the proposed surgery. Predictors of improved prognosis following metastasectomy are long disease-free interval, slow tumor doubling time, and complete resection. Malignancies with the best surgical outcomes are nonseminomatous germ cell tumor, colon cancer, renal cell carcinoma, and sarcoma. Option A depicts a poor operative candidate with a disease with poor outcomes (oral tongue cancer). Option B presents a patient with contralateral, extrathoracic disease and a malignancy of moderate outcomes following pulmonary metastases. Although option C describes a patient with a long disease-free interval and a malignancy with favorable outcomes following pulmonary metastasectomy, the patient has elevated serum markers and ought to be treated with systemic therapy first to attempt normalization of serum markers prior to proceeding with resection. Bilateral and repeated resections have not been demonstrated to negatively impact outcome in patients with metastatic colon cancer.
4. **Answer: A.** Isolated lung perfusion requires a thoracotomy, which may result in significant morbidity in patients with poor pulmonary function. In addition, ILuP has not been investigated in Phase III trials and should be restricted to institutions of specialization with active research protocols.
5. **Answer: B.** Computed tomography is the current standard for imaging pulmonary nodules. Plain radiography is not as sensitive as CT for small nodules; PET has poor sensitivity for nodules smaller than 10 mm and for certain histologies. Although PET/CT shows promise, its role has not been sufficiently studied yet.

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11

# Lung and Heart–Lung Transplantation

*Ashish S. Shah*

## KEY CONCEPTS

- Epidemiology
  - To date, more than 30,000 lung and 2600 heart–lung transplantations have been reported to the International Society of Heart and Lung Transplant Registry. Since 2005, bilateral lung transplant has been the most commonly performed procedure.
- Pathophysiology
  - Lung and heart–lung transplantation is performed for patients who have end-stage cardiopulmonary disease with no contraindications and have the potential to be rehabilitated completely. Most lung transplants are done for chronic obstructive pulmonary disease (COPD), cystic fibrosis, idiopathic pulmonary fibrosis, and pulmonary hypertension. Primary pulmonary hypertension and Eisenmenger syndrome are the most common indications for heart–lung transplantation.
- Clinical features
  - Candidates typically experience severe dyspnea, cyanosis, hemoptysis, or multiple hospitalizations and have New York Heart Association functional class III and IV status. Lung transplant candidates typically have a life expectancy of 24 to 36 months and are usually less than 75 years of age. Patients with COPD generally have a forced expiratory volume in 1 second ($FEV_1$) of less than 20 percent predicted, whereas patients with cystic fibrosis usually have an $FEV_1$ of less than 30 percent predicted, an increasing oxygen requirement, nutritional decline, and an increasing requirement for hospitalization. Patients with interstitial lung diseases may have a rapidly progressive decline with increasing oxygen requirements and reduced vital capacity. Candidates for heart–lung transplant have both pulmonary and cardiac disease and are typically under 65 years of age.
- Diagnostics
  - Candidates for lung and heart–lung transplants undergo an extensive workup to evaluate underlying cardiopulmonary function and exclude malignancy, active infection, end-organ dysfunction, and vascular disease. Diagnostic modalities include pulmonary function tests, endoscopy (especially bronchoscopy), echocardiography, cardiac catheterization, duplex ultrasonography, computed tomography and/or magnetic resonance imaging, serologic screens, and metabolic panels.
- Treatment
  - *Lung transplantation:* COPD, cystic fibrosis, idiopathic pulmonary fibrosis, and pulmonary hypertension.
  - *Heart–lung transplantation:* Eisenmenger syndrome, sarcoid with both cardiac and pulmonary involvement.
- Outcomes
  - Lung transplant survival rates are 82, 55, and 30 percent at 1, 5, and 10 years, respectively; best survival rates are among patients with cystic fibrosis. Significant spirometric improvement is immediate and plateaus at 6 to 12 months. For heart–lung transplantation, survival rates are 71 percent at 1 year. Early morbidity and mortality stem from technical complications, infections, and graft failure. Late complications are usually manifestations of bronchiolitis obliterans and malignancy.

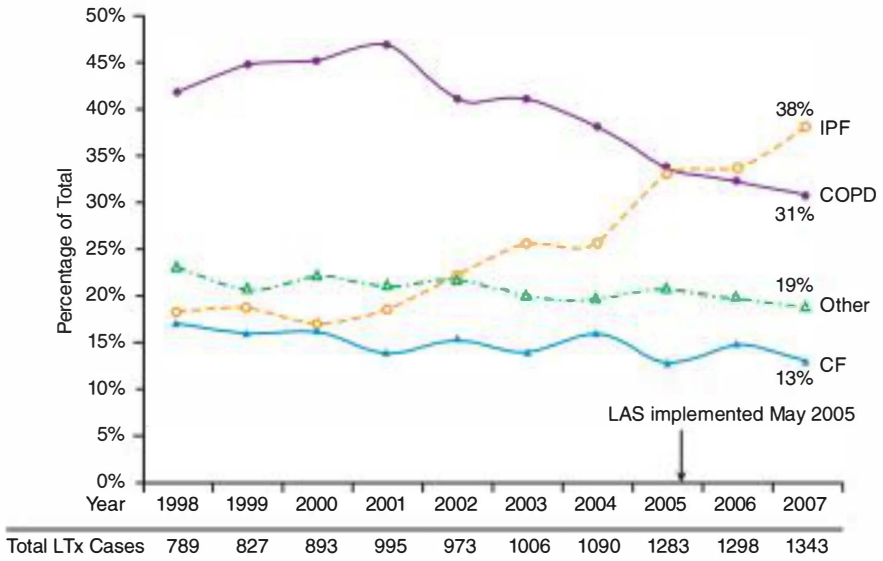



**FIGURE 11-1** Changing indication for lung transplant in the United States. Following implementation of the Lung Allocation Score system in 2005, there has been an increase in patients transplanted with the diagnosis of IPF. (Reproduced with permission from Weiss ES, Allen JG, Merlo CA, Conte JV, Shah AS. Survival after single versus bilateral lung transplantation for high-risk patients with pulmonary fibrosis. *Ann Thorac Surg* 2009; 88:1616–1625. Copyright Elsevier.)

## INTRODUCTION

Lung and heart–lung transplantation has emerged over the past several decades as an acceptable therapy for end-stage lung disease. Despite significant progress, lung transplantation remains a complex therapy that requires a multidisciplinary approach for successful outcomes. Moreover, it is increasingly clear that early postoperative events are associated with long-term complications. There are currently approximately 1800 and 70 patients awaiting lung and heart–lung transplant, respectively. In 2009, 1599 adult lung transplants were performed in the United States. In 2005, a new allocation policy was adopted in the United States. Patients are now assigned a Lung Allocation Score (LAS) based on clinical parameters. The score emphasizes transplant utility rather than wait-list time. It allows rapid allocation of organs to critically ill patients and decreasing allocation to less sick patients. As a result, patients are no longer listed just to accrue time. This has led to a significant reduction in the size of the active wait list (Fig. 11-1). The number of heart–lung transplant procedures has also declined.[1] Bilateral lung transplant has supplanted many of the indications. Nonetheless, a small group of patients remain excellent candidates for this unique procedure.

## HISTORY

In 1963, James Hardy performed the first human lung transplant.[2] This right single-lung transplant recipient died in 18 days with a functioning allograft. After the introduction of cyclosporine, Reitz and colleagues at Stanford performed the first combined heart–lung transplant.[3] In 1983, Joel Cooper successfully performed single-lung transplants in three patients.[4] By 1992, bilateral sequential lung transplantation supplanted en bloc double lung transplant, marking the modern era of lung transplantation.

## RECIPIENT SELECTION

Simply stated, lung transplant is indicated in patients with end-stage lung disease, with the purpose of increasing survival and improving quality of life. Recipient selection is critically important and may be complex, given the range of pathologies in candidates.

## ABSOLUTE CONTRAINDICATION

There are a number of absolute contraindications to lung transplantation as defined by the International Society of Heart and Lung Transplantation (ISHLT).[5] Patients should not have had a malignancy in the last 2 years, except for certain skin cancers. In patients with a history of cancer, a disease-free interval of at least 5 years is recommended. Candidates should not have untreatable end-organ dysfunction. This would include uncorrectable coronary artery disease, significant left-ventricular dysfunction, and end-stage liver disease. Patients with renal failure or significant insufficiency should not be considered unless combined with kidney transplant. Active viral infections are a contraindication and include hepatitis B, C, and HIV. Patients who are actively

using tobacco or abusing other drugs or alcohol should not be considered for transplant and should be abstinent for at least 6 months. Finally, significant psychosocial problems preclude transplantation.

## RELATIVE CONTRAINDICATIONS

With improving results, several centers have been emboldened to offer lung transplantation to a wider spectrum of patients. As a result, there are several relative contraindications to lung transplantation, and each center must decide the importance of each. Initially, an age cutoff for lung transplant had been proposed; however, several centers have transplanted patients over the age of 70 years with reasonable results. The national experience in this age group, however, is poor. Nonetheless, the ISHLT guidelines have set 65 years as the upper limit, and advanced age as a relative contraindication. Severely limited functional status and obesity lead to poor outcomes, and patients should actively participate in rehabilitation programs if possible, maintaining a body mass index (BMI) <30. Long-term steroids after transplant make severe osteoporosis a relative contraindication.[5]

## DISEASE-SPECIFIC INDICATIONS FOR TRANSPLANT

The ISHLT has established disease-specific guidelines summarized in Table 11-1. Controversy exists in transplantation for bronchoalveolar cell carcinoma. Since the disease recurs locally, lung transplantation has been used to treat these patients. Limited series have demonstrated acceptable short-term survival.[6] Primary, diseases do not recur except in sarcoid.

## DONOR SELECTION

There has been a significant liberalization of donor criteria over the past decade. The original criteria for what is considered a standard donor have given way to a more realistic set of criteria (Table 11-2). Ultimately, centers can accept or decline any organ for various reasons, but it is increasingly clear that donor characteristics have less to do with outcome than previously thought. Large database studies have found only donor tobacco use greater than 20 pack-years and age to be important risk factors.[7,8] Nonetheless, there are special considerations in lung transplantation. First, matching donor and recipient size is important. Oversized lungs can compromise hemodynamics early after transplant and have a long-term propensity of atelectasis. Height is clearly more important than weight, and gender is relevant when considering female recipients with fibrotic lung diseases. There are many ways to judge size matching ranging from simple height and weight ranges to estimating total lung capacity.[9] A simple rule is to use

### TABLE 11-1: Disease-specific Guidelines for Listing for Lung Transplantation

**Chronic obstructive pulmonary disease**
BODE index of 7 to 10 or at least one of the following:
- History of hospitalization for exacerbation associated with acute hypercapnia ($P_{CO_2}$ exceeding 50 mm Hg)
- Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy
- $FEV_1$, 20% and either DLCO, 20% or homogenous distribution of emphysema

**Idiopathic pulmonary fibrosis**
Histologic or radiographic evidence of UIP and any of the following:
- A DLCO, 39% predicted
- A 10% or greater decrement in FVC during 6 months of follow-up
- A decrease in pulse oximetry, 88% during a 6-min-walk test
- Honeycombing on HRCT (fibrosis score 0.2)

**Cystic fibrosis**
$FEV_1$, 30% of predicted, or rapidly declining lung function if $FEV_1$, 30% (females and patients, 18 years of age have a poorer prognosis; consider earlier listing) and/or any of the following:
- Increasing oxygen requirements
- Hypercapnia
- Pulmonary hypertension

**Idiopathic pulmonary arterial hypertension**
Persistent NYHA Class III or IV on maximal medical therapy
- Low (350 m) or declining 6-min-walk test
- Failing therapy with intravenous epoprostenol, or equivalent.
- Cardiac index of <2 L/min/m²
- Right atrial pressure >15 mm Hg

**Sarcoidosis**
NYHA functional class III or IV and any of the following:
- Hypoxemia at rest
- Pulmonary hypertension
- Elevated right atrial pressure >15 mm Hg

Definition of abbreviations: BODE 5 body mass index, airflow obstruction, dyspnea, and exercise capacity; HRCT 5 high-resolution computed t omography; NYHA 5 New York Heart Association; UIP 5

### TABLE 11-2: Donor Criteria

**Standard**
Age <55
ABO compatible
Clear chest X-RAY
Arterial oxygen pressure >300 on inspired oxygen of 100% and positive end-expiratory pressure of 5 cm $H_2O$.
<20-pack-year smoking history
Absence of chest trauma
Absence of aspiration
Gram stain free of bacteria

**Realistic**
Age <65
>20-pack-year smoking history with clear Chest CT and no functional impairment
Positive donor sputum culture (pansensitive organism)
Unilateral infiltrate

donors who are no more than 4 inches in recipient height for most lung diseases. However, cystic fibrosis and chronic obstructive pulmonary disease (COPD) can usually accommodate much larger donor sizes (as much as 12 inches in difference). Moreover, oversized donors may be trimmed with multiple wedge resections or even anatomic resection ex vivo to allow transplantation in small recipients.

There has been growing interest in using non-heart beating donors (DCD) for lung transplant. Lungs remain metabolically stable without circulation for up to an hour when ventilated. As a result, DCD donors may yield functional lungs without brain death-related injury. The initial experience is acceptable but the number of actual donors added to the pool may be limited.[10] Similarly, there is a growing experience with ex vivo perfusion of potential donors to rehabilitate unacceptable lungs.[11,12]

## DONOR ASSESSMENT

When the recovery team arrives at the donor hospital, review of the imaging and documentation should be performed as well as the mechanics on the ventilator. Bronchoscopy should be performed by the recovery team to assess for intraluminal masses and secretion quality. Purulent secretions that cannot be cleared bronchoscopically represent a relative contraindication to donation.

After median sternotomy and opening of the pleural spaces, the lungs should be palpated for masses and the compliance assessed by simple observation. Frequently, obese donors will have much better mechanics when the chest is opened. The pericardium is then opened. The superior vena cava (SVC) should be mobilized completely to prevent injury to the right pulmonary artery. We prefer separation of the aorta and main PA as well. In donors with small atria, modest dissection of Sondergaard's groove can help the right-sided left atrial cuff. A final arterial blood gas is obtained under these ideal conditions. If single-lung transplantation is planned, then blood gases may be obtained from individual pulmonary veins to asses each lung.

The main pulmonary artery should be cannulated with an angled 20-F aortic cannula. Some institutions strongly feel to direct the cannula toward the pulmonary valve to evenly distribute preservation solution, but we have not found this to be clinically important. Prior to cross-clamping, the teams should decide where venting of the left atrium should occur. If the heart is to be recovered, then the left atrial appendage is preferable. To preserve left atrial appendage function, some centers will rather incise along Sondergaard's groove. The SVC is ligated. Prostaglandin is injected into the main pulmonary artery. The inferior vena cava (IVC) and left atrium are then vented. The aorta is cross-clamped, and the preservation solution is delivered. When a heart–lung bloc is recovered, both cardioplegia and pulmonary preservation solution are used.

During infusion of the preservation solution, we continue gentle ventilation with inspired oxygen and monitor the effluent from the left atrial venting site. We infuse 4 L antegrade in all donors. The donor heart is then removed. Special attention should be made to the left atrial cuffs. These may be taken as two discrete cuffs or one single. The right-sided cuff can be compromised, and dissecting Sondergaard's groove prior to recovery can help prevent this problem.

Once the heart is out, we proceed with retrograde perfusion of the donor lungs via the pulmonary vein orifices (500 $cm^3$ in each). Low-potassium dextran has emerged as the most common and currently best preservation solution. This is particularly true for high-risk lung transplant recipients.[13] The maximal acceptable ischemic time for lungs is between 6 and 8 hours.

The dissection then proceeds outside the pericardium and anterior or ventral to the esophagus. The left and right pleura are then incised along the esophagus as far cephalad as possible. On the right, the azygous vein is transected, and on the left, the aorta is transected. The airway is then isolated between the aorta and SVC and tissue cleared laterally. The final attachments are usually at the level of the carina, and the airway is stapled with a modest level of inflation. We have never found it necessary to take the esophagus with the bloc but some centers work in this plane to prevent injury to the allograft.

The lungs are then inspected for damage and packed in iced saline and preservation solution. In the case of single-lung transplantation, the bloc should be divided prior to packaging.

## PROCEDURE SELECTION

### Single Versus Bilateral Lung Transplant

Bilateral lung transplant is necessary in suppurative lung diseases and in pulmonary hypertension. Single-lung transplantation can be used in patients with interstitial or fibrotic lung disease and emphysema. However, there is some evidence that bilateral lung transplant may have advantages in COPD and IPF. Although patients with IPF have similar outcomes with single or bilateral lungs, high-risk IPF patients may benefit from bilateral lung transplant.[14–16] For COPD, there is a modest survival and potential immunologic advantage. Certainly, bilateral lung transplant in emphysema eliminates complications of the native lung including hyperinflation, pneumothorax, differential compliance, and long-term risk of malignancy.

### Heart–Lung Transplant

Patients with end-stage heart and lung disease are candidates for combined heart–lung transplant. Although primary or secondary pulmonary hypertension is no longer an exclusive indication for heart–lung transplant, patients with biventricular failure or unreconstructable heart disease are reasonable candidates. Occasionally, cystic



**FIGURE 11-2** Patient positioning for a clamshell approach. (Reproduced with permission from Davis RD. Bilateral sequential lung transplantation. *Oper Tech Thorac Cardiovasc Surg* 2007;12:57–72. Copyright Elsevier.)

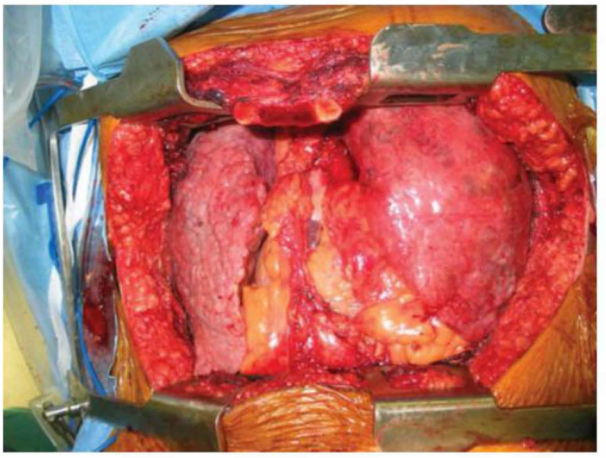


**FIGURE 11-3** Exposure after clamshell or bilateral trans-sternal thoracotomy.

fibrosis, primary pulmonary hypertension, and sarcoid patients will have biventricular failure.

## OPERATIVE TECHNIQUES

### Bilateral Sequential Lung Transplantation

After the induction of anesthesia, the recipient is intubated with a double-lumen endotracheal tube whenever possible. Even when cardiopulmonary bypass (CPB) is planned, double-lumen tubes allow for flexibility in dissection and reperfusion management. Pulmonary artery catheters are routinely as well as radial and femoral arterial lines. The femoral arterial line allows more consistent blood pressure measurement. It also allows access to place intra-aortic balloon pumps and extracorporeal circulation cannulae. The arms are placed over the head in arm stirrups (Fig. 11-2). Bilateral anterolateral thoractomies are performed through the fourth or fifth interspace and across the sternum (Fig. 11-3). Some centers have used sternal-sparing techniques or bilateral posterolateral thoractomies. Median sternotomy may also be used; however, access to pleural adhesions may be limited.

Once the retrosternal mediastinal adhesions are cleared cephalad and caudad, the intercostals muscles are incised with cautery generously. Two retractors are placed and the exposure is excellent. Attention is turned to the right lung first to isolate the inferior and superior veins, and then the pulmonary artery. The left lung is similarly dissected. In the presence of dense adhesions or severe bleeding, an intrapericardial dissection may allow safer isolation, and an extrapleural dissection may cause less bleeding. When the donor lungs have arrived, the less perfused lung (based on preoperative ventilation/perfusion scan) is removed first using vascular staplers. The bronchus is finally stapled. The hilar structures are further dissected into the pericardium to allow for maximal length and minimal cardiac manipulation.

The donor lung is placed in the chest, wrapped in an iced sponge. The airway is then anastomosed with running prolene or PDS. This may be done with a telescoping or end-to-end technique. The membranous trachea may be approximated with a continuous suture and the cartilaginous with an interrupted technique. We use a simple running, end-to-end technique with satisfactory results.

The pulmonary artery is approximated next, followed by the pulmonary veins. The allograft is deaired through the atrial anastomosis with partial opening of the pulmonary artery clamp. With good hemostasis, the lung is inflated with room air and reperfusion performed in a controlled manner over 10 minutes.

The left lung is implanted in a similar fashion. However, exposure to the left hilum may be more difficult due to the heart and small left atrium found in women and fibrotic lung disease patients. Several techniques can be used to improve exposure. The pericardium may be opened and the left ventricular apex displaced medially similar to off-pump techniques. Alternatively, the surgeon may decide to go on CPB centrally to safely implant the left lung with stable hemodynamics. CPB may also be used if the first lung is overcirculated or not functioning adequately to support the patient.

The left lung may also be implanted first if necessary to maintain cardiopulmonary stability. It is critically important to identify the phrenic nerves on both sides and not to injure them. Less concerning is injury to the recurrent nerve on the left. Both vagus nerves may also be injured as they run dorsal to the airways.

With both lungs reperfused and the cardiopulmonary status stable, the wound is closed with several chest tubes and three sternal wires. The endotracheal tube is exchanged for a single-lumen tube, and final bronchoscopy is performed to make sure that there is no intraluminal obstruction, anastomotic problems, or lobar torsion.

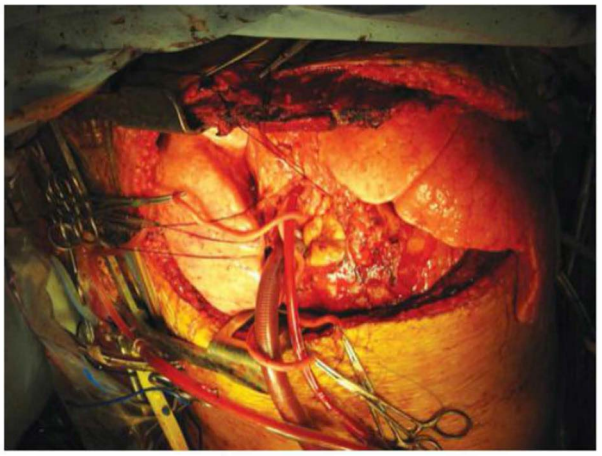


FIGURE 11-4 A patient following lung transplant using cardiopulmonary bypass. The patient is centrally cannulated.

## USE OF CARDIOPULMONARY BYPASS

CPB may be used selectively (pulmonary hypertension and patients unable to tolerate single-lung ventilation) or routinely. Typically, the aorta and right atrium are cannulated, and the patient is placed on normothermic bypass (Fig. 11-4). If concomitant cardiac surgery is necessary, this may be done prior to lung implant. Reperfusion on CPB is even more controlled where the goal is to keep the mean pulmonary artery pressure low during the 10-minute period. We use a period of modified ultrafiltration as well. In this technique, after separation from bypass, the patient's blood is withdrawn from the aorta and reinfused into the venous cannula after running through a hemoconcentrator. The purpose is to remove extravascular fluid and inflammatory cytokines. Alternatively, there is some evidence that CPB use is associated with increased risk of primary graft dysfunction and blood product usage, but less lung manipulation and soilage in suppurative lung disease.[17,18] Our center uses CPB selectively, but with a low threshold. We initiate CPB for one lung when the first allograft is overcirculated or functioning poorly, and when the left atrium on the left side is small.

### Single-Lung Transplant

Single-lung transplant uses similar anastomoses (bronchus, PA, and LA) and may be performed through posterolateral thoracotomy or anterolateral approach.

### Heart–Lung Transplant

Heart–lung transplant involves the following connections: trachea, aorta, SVC, and IVC. As a result, either median sternotomy or clamshell may be used. In patients with potential pleural adhesions or previous sternotomy, we prefer the clamshell incision. The recipient explants may be difficult, but the patient is cannulated via the aorta, SVC, and IVC. The cross-clamp is applied, and the heart is removed as in heart transplant. The phrenic nerves are identified and windows created dorsal to both. The pulmonary artery and vein may be divided with staplers or simply transected with the cautery, but the airway should be stapled to limit contamination. The airways are then dissected back to the trachea and then transected well below the innominate vein. The remaining cardiac structures may be resected or left behind. Care should be taken in the area of the recurrent nerve, and we usually leave posterior or dorsal wall of the pulmonary artery near the ligamentum to minimize the risk. Special attention should be paid to hemostasis at this point before proceeding with implantation. The allograft is then brought to the field, and both lungs are placed in anatomic position. The tracheal anastomosis constructed first with 4-0 prolene or PDS, followed by the IVC and the aorta. The cross-clamp is then removed and the SVC reconstructed. The lungs are inflated with room air during reperfusion and separation from bypass. We use a period of modified ultrafiltration prior to reversing the heparin. Typically, the cardiac function is good, and the patient may be managed as a standard lung transplant patient.

## POSTOPERATIVE CARE

Managing the postoperative lung transplant patient demands a unique focus on protecting the allograft while supporting the patient. Transplanted lungs do not have lymphatic drainage, are susceptible to excess extra vascular fluid, and have a propensity for oxidative injury. Moreover, a significant percentage of lungs will have varying degrees of graft dysfunction that need to be managed carefully. From a ventilatory perspective, the recipient is maintained at the lowest fraction of inspired oxygen ($Fio_2$) possible. The purpose is to minimize oxidative stress, but to also provide an early warning system for graft dysfunction. Keeping the $Fio_2$ low will lead to desaturation if there is a problem and direct an evaluation in a timely manner. We use a pressure-control mode of ventilation, maintain a positive end-expiratory pressure (PEEP) of 8, and try to achieve tidal volume of 8 $cm^3/kg$. Ventilator settings are adjusted to maintain a $Pao_2$ >70 and pH >7.3. After a period of stabilization, the patient may be extubated within 24 hours. Some patients, particularly after single-lung transplant, may be extubated in the operating room. Alternatively, some allografts need prolonged positive pressure and can develop severe pulmonary edema after extubation. Anecdotally, this is a bigger problem in patients with primary pulmonary hypertension, and we are much slower to wean these patients. We also liberally place tracheostomy tubes and use noninvasive ventilation when patients are at risk for prolonged ventilation or reintubation. Pain control is critical and we place an epidural catheter in *all* patients postoperatively. This is done while intubated and when any coagulopathy is resolved. Patients are extubated after toilet

bronchoscopy and when meeting conventional criteria for extubation. Volume status is maintained with central venous pressure (CVP) <8 as tolerated, with liberal use of adrenergic agents and diuretics. We used dopamine, vasopressin, and epinephrine preferentially. Patients with poor respiratory effort, allograft dysfunction, and phrenic nerve dysfunction undergo early tracheostomy. Noninvasive ventilation is also used liberally in the early postoperative period if the mechanism of respiratory failure is easily reversible.

Once extubated, vigilance is critical. The allograft is denervated and mucociliary clearance is impaired. As a result, patients need to work hard on pulmonary toilet. We liberally use bronchoscopy to clear airways. Since pharyngeal dysfunction is common postoperatively, all of our patients undergo formal video fluoroscopic swallow studies. Many patients will aspirate thin liquids for 1 to 2 weeks postoperatively.[19] Patients with preoperative malnutrition, severe swallowing problems, or gastroparesis receive percutaneous gastrojejunostomy feeding tubes.

**TABLE 11-3: Rejection Table**

**Acute rejection**
Grade 0—none
Grade 1—minimal
Grade 2—mild
Grade 3—moderate
Grade 4—Severe

**Airway inflammation**
Grade 0—none
Grade 1R—low grade
Grade 2R—high grade
Grade X—ungradable

**Chronic airway rejection—obliterative bronchiolitis**
0—absent
1—present

**Chronic vascular rejection—accelerated graft vascular sclerosis**

## IMMUNE SUPPRESSION

Standard immune suppression for clinical lung transplantation includes a calcinuerin inhibitor (CI), purine synthesis inhibitor, and steroids. Cyclosporine and tarcrolimus have similar efficacy, but tacrolimus is the most commonly used CI in the United States. Azathioprine and mycophenolate (MMF) seem to have similar efficacy as well. MMF does have some advantages in patients with preformed anti-HLA antibodies[20] and is the most commonly used agent in the United States. Induction agents, such as Thymoglobulin, Basiliximab, and Azulatamab, are also commonly used in 60 percent of US transplant patients.[1] There is some evidence that these agents reduce acute rejection episodes in the first year, but with no long-term benefits. Azulatamab has been used to limit immune suppression in a series from the University of Pittsburgh.[21] A small series of patients have also benefited from inhaled cyclosporine.[22]

## POSTOPERATIVE COMPLICATIONS

### Infection

There are four broad categories of postoperative infections. The first is bacterial. Patients may develop pneumonias from donor-acquired organisms or native pathogens particularly in CF patients. Perioperative antibiotics should be directed toward such organisms for a prolonged period (at least 2 weeks). Surveillance bronchoscopy postoperatively should also include cultures. The second is viral. The most common is cytomegalovirus, and patients receive prophylactic ganciclovir for donor and recipient mismatch. The rare CMV naïve donor and recipient may receive Valcyte. Other respiratory viruses should be cultured in all BALs. Fungal infections are the third troublesome pathogen. CF patients in particular are at high risk; however, in the setting of immune suppression, any patient can be infected or colonized. We use inhaled amphotericin in all recipients during their hospitalization and oral antifungals as directed by cultures. Finally, patients are at risk for pneumocystis infection and receive lifelong bactrim for prophylaxis.

## REJECTION

### Acute Rejection

Acute rejection is unfortunately common after lung transplantation. The incidence in the first year is typically 30 to 50 percent depending on the definition and severity.[23] Cellular rejection is far more common, and the diagnosis is made by transbronchial biopsy. Symptoms may be similar to infection and include fever, dyspnea, and decline in spirometry. Less common is antibody-mediated rejection that may manifest in similar ways or fulminant vasculitis and capillary leak syndrome. Table 11-3 summarizes the current ISHLT rejection criteria. For cellular rejection (A2 or greater) treatment is high-dose steroids. For humoral rejection, plasmapheresis, rituximab, and IVIG are all used at JHH. Patients with refractory rejection may have campath or thymoglobulin. Multiple episodes of acute rejection have been implicated in the development of chronic allograft function. Figure 11-5 is a representative specimen of severe A3 acute cellular rejection.

### Chronic Rejection

Chronic rejection and chronic allograft dysfunction are likely the final common pathway of multiple injuries and agents. Acute rejection, viral infection, antibody-mediated injury, and, more recently, gastroesophageal reflux have all been postulated to cause a narrowing of small airways leading to

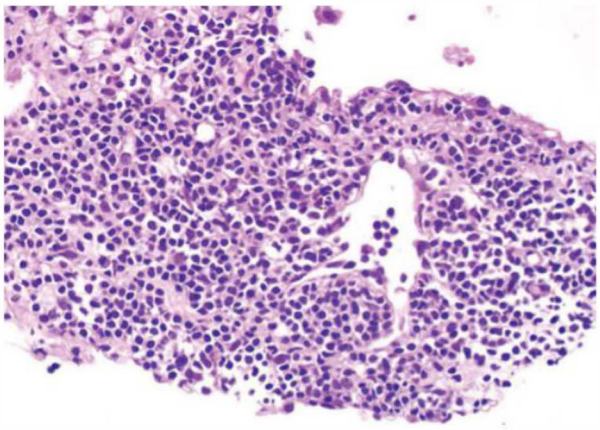


FIGURE 11-5 Representative histology of severe A3 acute cellular rejection.

airflow obstruction and allograft failure. Failing allografts with a decline of $FEV_1$ >20 percent are considered as having the bronchiolitis obliterans syndrome (BOS); histologic confirmation may be done with biopsy. At 5 years, nearly 50 percent of recipients have BOS.[23] Treatment is limited and includes azithromycin, fundoplication, or retransplantation. It is currently impossible to predict which patients will improve or stabilize their allograft function with any of these therapies and studies are ongoing. The Washington University group has postulated that early primary graft dysfunction leads to anti-HLA antibodies that in turn injure the allograft and ultimately lead to BOS.[24]

### AIRWAY COMPLICATIONS

The early surgical experience in human lung transplant was plagued with airway complications. In particular, airway dehiscence was a dreaded and common complication leading to death. With surgical and medical refinements, dehiscence in uncommon but stenosis has emerged as a persistent problem. Patients can present with anastomotic problems or distal airway disease. The etiology remains unclear and is likely a spectrum of problems that may be technical or microvascular in nature. Fortunately, a number of techniques exist to remedy airway problems. Simple balloon dilatation, stents (covered and uncovered), brachy, cryo, and antineoplastic therapies are all used. Many patients will require multiple interventions, and it is important to maintain a close follow-up (Fig. 11-6).[25]

## SPECIAL CONSIDERATION FOR HEART–LUNG TRANSPLANT

Heart–lung transplant patients are managed like lung transplant patients. The cardiac function is consistently good, although some patients may experience brady arrhythmias. Interestingly, the lungs may be rejected without synchronous cardiac rejection. Both organs are typically biopsied in the follow-up period. Heart–lung patients appear to have the same risk of BOS and coronary vasculopathy as isolated lung transplant patients.[26,27]

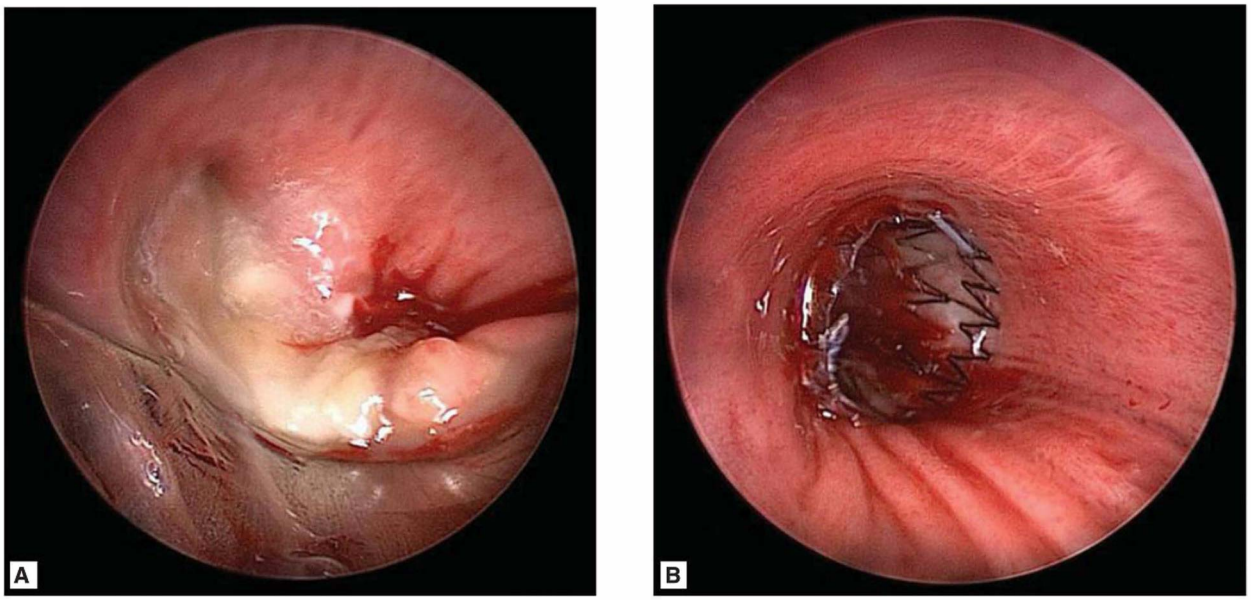



FIGURE 11-6 **A.** Bronchoscopic appearance of posttransplant airway stenosis. **B.** Results of dilatation and stenting.

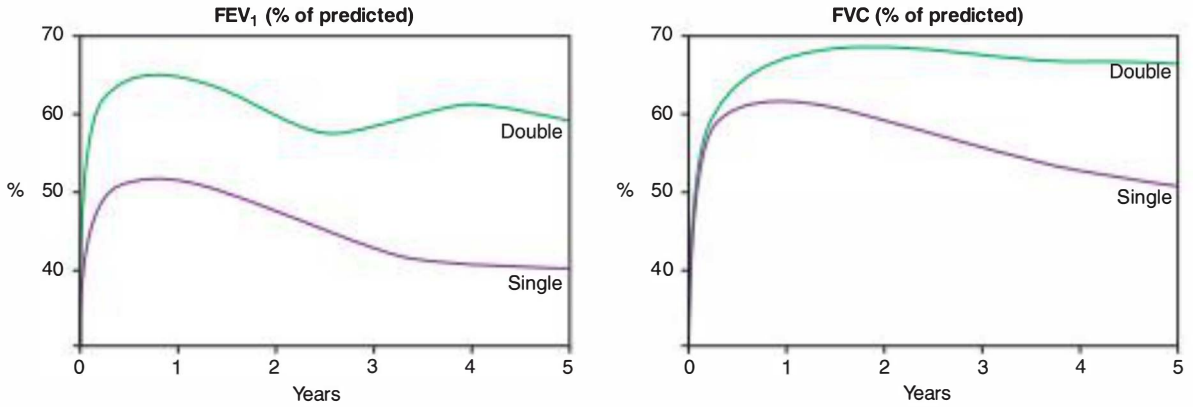



**FIGURE 11-7** Actual spirometric outcomes following double- or single-lung transplant over time. (Reproduced with permission from Mason DP, Rajeswaran J, Murthy SC, et al. Spirometery after transplantation: How much better are two lungs than one? *Ann Thorac Surg* 2008;85:1193–1201. Copyright Elsevier.)

## OUTCOMES/RESULTS

Short-term outcomes have improved significantly over the past 20 years. Current unadjusted 90-day survival is 90 percent and 1-, 5-, and 10-year survival is 83, 54, and 29 percent, respectively.[1] In the short term, patients with pulmonary hypertension have worse outcomes than other diseases. However, over time, pulmonary fibrosis emerges with worse outcomes and then at 10 years, emphysema has the lowest long-term survival. Patients with higher LAS appear to have higher 1-year mortality posttransplant.[28] Moreover, patients on mechanical ventilation and extracorporeal membrane oxygenation have significantly worse postoperative outcomes.[29] This should be kept in context with the high likelihood of death without transplant. Survival after heart–lung transplant is similar.

Spriometry is currently the basic measure of lung performance, and patients achieve maximal function after 6 months to 1 year. Bilateral lung transplant patients have better spirometric lung function than single lung (Fig. 11-7).[30]

## BRONCHIOLITIS OBLITERANS SYNDROME

BOS is the long-term form of allograft dysfunction. The pathologic lesion is obliteration of bronchioles with airflow obstruction and decline in spirometry. The exact cause is unknown, but there are a number of putative mechanisms including CMV, chronic aspiration, and reflux, as well as antibody-mediated injury. It represents the final common pathway of airway injury leading to a maladaptive reparative response.[24,31–35] Treatment is limited to augmenting immune suppression, surgical correction of reflux, and azithromycin. There is likely a spectrum on BOS that may or may not be responsive to therapy, and certainly timing of therapy and onset of BOS will determine efficacy. Retransplant is also an option in properly selected patients.

## SPECIAL ISSUES

### Sensitized Patients

Preformed antibodies against HLA loci create challenges both pre- and posttransplant. These antibodies form the basis of prospective crossmatching, but with modern laboratory techniques, centers are moving away from tissue crossmatching. Current flow cytometric methods allow for sensitive detection and specification of the antibodies. All donors are typed, and a comparison is made between antibodies and antigens. This is virtual crossmatching. Without the need for actual tissue crossmatching, recipients have shorter wait times.[36] Since 1997, the presence of anti-HLA antibodies is no longer a risk factor for early death in lung transplantation.[37] However, there appears to be a relationship with the de novo development of antibodies and risk of chronic rejection.[38] Sensitized patients are managed with multiple therapies including IVIG, plasmapheresis, and rituximab.[39,40]

## REFLUX AND ASPIRATION

As surgical challenges have been overcome, attention has turned to long-term failure. Patients with significant gastroesophageal reflux appear to have worse outcomes. Moreover, posttransplant, reflux worsens in a subset of patients. This is likely a consequence of vagal injury, immune suppression, and postoperative changes. Led by work at Duke University, an aggressive approach to correcting reflux with fundoplication has proven to be safe, effective, and, in many patients, to stabilize and even improve allograft function. Unfortunately, the results with posttransplant fundoplication have been inconsistent, and future studies are needed to better define timing of the procedure.[19,41–45]

**TABLE 11-4: International Society for Heart and Lung Transplantation Primary Graft Dysfunction Grading Schema**

| Grade | $Pao_2/Fio_2$ | Radiographic Infiltrates Consistent with Pulmonary Edema |
|---|---|---|
| 0 | >300 | Absent |
| 1 | >300 | Present |
| 2 | 200–300 | Present |
| 3 | <200 | Present |

## PRIMARY GRAFT DYSFUNCTION

Early postoperative allograft failure is formally described as primary graft dysfunction. There is a range of failures that is defined by the $Pao_2/Fio_2$ ratio (Table 11-4). The injury has all the hallmarks of acute respiratory distress syndrome (hypoxemia, pulmonary hypertension, and poor compliance) but differs in that it usually improves within 72 hours. Support includes protective ventilation strategies and extracorporeal membrane oxygenation. It is important to rule out mechanical problems including pulmonary vein thrombosis or stenosis and immunologic injury. Severe PGD has a mortality of 30 to 40 percent, and survivors are at increased risk of long-term allograft dysfunction. There have been several studies looking at risk factors for PGD and include clinical and biochemical variables.[46–48] Clinically, important variables include pulmonary hypertension, prolonged ischemic time, and blood product transfusion.

## RETRANSPLANTATION

When allograft dysfunction is irreversible and other end-organ dysfunction is absent, retransplantation may be the only option. It accounts for approximately 5 percent of all transplants and has an unadjusted 1-year survival of 70 percent. In the United States, most retransplants are bilateral lung transplants, and 60 percent are done for BOS. A small percentage of patients with early allograft failure may undergo retransplant, but with inferior results. Mean time to retransplant in the United States is 1500 days.[1]

## LUNG ALLOCATION SCORE

Since 2005, donor lungs in the United States have been allocated by the LAS. The score is generated from several clinical variables and prioritizes patients (Table 11-5). The score (0–100) was designed to maximize utility-minimizing wait list mortality and maximizing posttransplant survival. After implementation, waiting time has decreased and mortality has remained unchanged or slightly lower. Postoperative survival is unchanged in most patients; however, patients with LAS >44 appear to have worse 1-year survival. The score is revised periodically.[28,49–51]

**TABLE 11-5: Components of LAS**

| |
|---|
| Age |
| BMI |
| FVC % predicted |
| Functional status |
| Diagnosis |
| PA systolic pressure and mean |
| Diabetes |
| Mechanical ventilation |
| Oxygen requirement |
| 6-min-walk distance |
| Serum creatinine |
| Change in $CO_2$ |

## CONCLUSION

Lung and heart–lung transplantation is a complex, but effective therapy for patients with end-stage lung disease. Future work in the field will continue focusing on improving early allograft performance and further understanding long-term allograft dysfunction.

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## LUNG AND HEART–LUNG TRANSPLANTATION BOARD REVIEW QUESTIONS (CHAPTER 11)

1. Which of the following is not a contraindication to lung transplantation?
   A. Disease-free interval of at least 10 years from malignancy
   B. Uncorrectable coronary artery disease
   C. Significant left ventricular dysfunction
   D. Renal failure
   E. Current tobacco use

2. Which is correct regarding lung procurement?
   A. Prostaglandin is injected after aortic cross-clamping.
   B. Gentle ventilation is continued during infusion of lung preservation solution.
   C. Retrograde perfusion of the lungs is discontinued before the heart is removed.
   D. The maximal acceptable ischemic time is 8 to 12 hours.
   E. The lungs are deflated prior to airway division.

3. Which is correct regarding donor selection criteria?
   A. Greater than 20 pack-year tobacco history is an absolute contraindication
   B. Severe multilobar contusion is acceptable
   C. Active non-central nervous system malignancy is acceptable
   D. Sputum culture positive with multidrug resistant organism
   E. Greater than 20 pack-year tobacco history is associated with increased long term risk of death

4. Which is true regarding outcomes after lung transplantation?
   A. Survival at 5 years exceeds 50 percent
   B. Patients with pulmonary hypertension have the best short-term outcomes.
   C. Patients with pulmonary fibrosis have the best long-term outcomes.
   D. At 10 years, those patients with emphysema have the best survival.
   E. Patients requiring mechanical ventilation prior to transplantation have equivalent survival.

5. Which grade is correct?
   A. Acute rejection, minimal = 2
   B. Acute rejection, severe = 5
   C. Airway inflammation, high grade = 1R
   D. Airway inflammation, ungradeable = X
   E. Chronic airway rejection, minimal = 1

## ANSWERS

1. **Answer: A.** A disease-free interval of at least 5 years from malignancy is required for listing for lung transplantation. Uncorrectable coronary artery disease, significant left ventricular dysfunction, renal failure or severe renal insufficiency, and active tobacco use are all absolute contraindications.

2. **Answer: B.** Gentle ventilation is continued during infusion of lung preservation solution. Prostaglandin is injected into the pulmonary artery prior to aortic cross-clamping. Retrograde perfusion of the lungs is continued after the heart is removed. The lungs are inflated prior to airway division. The maximal acceptable ischemic time is 6 to 8 hours.

3. **Answer: E.** Modern lung transplantation has seen a dramatic liberalization of donor criteria. Essentially any donor regardless of age with reasonable compliance, size matching, and $Pao_2$ >200 on an $Fio_2$ of 100% may be utilized for transplant. There are several relative contraindications such as active malignancy, Hepatitis C and HIV. Donor tobacco use is not an absolute contraindication, though heavy smoking is associated with long term risk of death particularly in patients with fibrotic lung disease.

4. **Answer: A.** Overall, a 5-year survival for lung transplantation is about 54 percent. Patients with pulmonary hypertension have the worst short-term outcomes. At midterm, patients with pulmonary fibrosis have the worst outcomes, and at 10 years, those with emphysema have the lowest survival. Patients requiring mechanical ventilation or ECMO have significantly worse outcomes.

5. **Answer: D.** Ungradeable airway inflammation is grade X. Minimal acute rejection is grade 1 and severe acute rejection is grade 4. Chronic airway rejection is either absent or present.

12

# Esophageal Physiology, Function Tests, and Endoscopic Techniques

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**KEY CONCEPTS**

- Physiology
  - The basic function of the esophagus is to propagate a bolus from the oropharynx to the stomach.
  - The coordination of esophageal muscle contractions, vagal innervation, and sphincter relaxation allows this event to occur.
- Function tests
  - Primary esophageal motility disorders can be diagnosed using conventional- or high-resolution manometry.
  - Various systems are available for reflux testing including 24-hour catheter-based pH monitoring, wireless capsule pH testing, and combined pH impedance.
- Endoscopic techniques
  - High-resolution endoscopy, chromoendoscopy, narrow band imaging, and confocal endomicroscopy are techniques that enhance the esophageal mucosa, improving diagnostic yield in Barrett's esophagus (BE) and early esophageal cancer.
  - Endoscopic ultrasound adds imaging from adjacent structures, and is useful for staging and fine-needle aspiration.
  - Multiple ablative techniques are now available for BE and early esophageal cancer, and include endoscopic mucosal resection, photodynamic therapy, radiofrequency ablation, cryotherapy, and endoscopic mucosal dissection.

## PHYSIOLOGY

Although the basic function of the esophagus is to simply propagate a bolus of food from the oropharynx to the stomach, the execution of this function remains complex. Ultimately, the swallow mechanism is a dynamic process between the muscles of the esophagus and its neural innervation, and involves the interplay between the upper esophageal sphincters (UESs) and lower esophageal sphincters (LESs).

The esophagus is a hollow tube, usually between 17 and 30 cm but averaging 23 cm.[1] At the proximal end is the UES, which is approximately 1 cm in length. The UES is composed of striated cervical esophageal muscle, the cricopharyngeus, and the inferior pharyngeal constrictor muscles. The superior and inferior hyoid muscles and superior pharyngeal muscles also help facilitate UES opening. Innervation of the UES arises from branches of the vagus nerve stemming from the nucleus ambiguus. Tonic closure of the UES functions to prevent insufflation of air during inspiration and esophagopharyngeal reflux. Intermittent relaxation of the UES allows bolus transit and venting (belching).

The esophageal body is composed of two different types of myocytes. Although somewhat variable, in general, the proximal third of the esophagus is striated muscle and the distal two-thirds composed of smooth muscle. The transition is not abrupt, and thus there is a short segment in which the muscles fibers are mixed. The arrangement is such that there is an outer longitudinal muscle layer and an inner circular muscle layer. This arrangement facilitates peristalsis, which will be discussed below.

Between the longitudinal and circular muscle layers lies the myenteric or Auerbach's plexus. This network of neurons

contains ganglia arising from the vagus nerve, although the concentration of ganglia affecting the smooth muscle portion is higher than the striated muscle portion. Ganglia innervating striated muscle stem from the nucleus ambiguus while ganglia innervating smooth muscle stem from the dorsal motor nucleus of the vagus. The neurotransmitter acetylcholine plays a role in activation of both striated and smooth muscles in the esophagus. Acetylcholine released by nerve endings activates the esophageal striated muscle. Postganglionic neurons in the distal esophagus activate smooth muscle cells by releasing acetylcholine. Inhibitory innervation of esophageal smooth muscle, which induces relaxation, is achieved by the release of nitric oxide (NO) and vasoactive intestinal polypeptide (VIP) from postganglionic nerve endings. The myenteric plexus is interconnected with Meissner's plexus, which is located in the submucosa and is responsible for innervation of the circular muscle layer and muscularis mucosa.

Sensory information is relayed in a dual manner via both vagal and spinal nerves. Esophageal sensation is extremely complex and beyond the scope of this chapter. In short, sensory information in the esophagus is relayed from either muscular afferent receptors or mucosal afferent receptors. In general, muscular afferent fibers respond to intraluminal distention. The pressure threshold leading to sensory nerve firing, and the rate of spontaneous firing, differs among vagal and spinal afferent neurons. In contrast, mucosal afferent fibers do not respond to distention but rather touch and chemical irritation by acid, bile, and other agents.[2]

The LES is a 2- to 4-cm high-pressure zone that provides a barrier between the distal tubular esophagus and stomach, composed of intrinsic circular muscles of the esophagus and extrinsic muscles from the crural diaphragm. Motor innervation again stems from the vagus nerve with preganglionic nerves releasing acetylcholine. The LES contracts in response to postganglionic excitatory neurons releasing acetylcholine. The LES relaxes with postganglionic inhibitory neurons releasing NO or VIP. The LES is tonically contracted and relaxes via reflex mechanisms in response to a swallow. The LES also relaxes in response to vomiting, belching, rumination, and transient LES relaxations (TLESRs). TLESRs are seen in normal patients and are increased in patients with gastroesophageal reflux disease (GERD). TLESRs also increase in response to gastric distention via reflex pathways.

Bolus transport occurs with peristalsis of the esophagus. Voluntary oropharyngeal deglutition triggers UES relaxation. Once the bolus enters the esophagus, the UES closes and the esophageal phase of swallowing takes over. The swallow event triggers primary peristalsis, or sequential esophageal muscle contractions, which occlude the esophageal lumen. Primary peristalsis propels the bolus forward down the esophagus, and a pressure of at least 20 mm Hg is needed to propel the bolus forward. Contraction of the longitudinal muscles also occurs, shortening the esophagus by approximately 2 cm. The peristaltic wave has a velocity of 3 cm/s in the upper esophagus, 5 cm/s in midesophagus, and 2.5 cm/s in the lower esophagus. With multiple rapid swallows, peristalsis remains inhibited until the last swallow. The control of primary peristalsis is centrally mediated.

Secondary peristalsis is triggered with luminal distention for the purpose of clearing residual bolus material due to ineffective primary peristalsis or reflux events. Pharyngeal contraction and UES relaxation are not seen in secondary peristalsis. The control of secondary peristalsis is intrinsic to the esophagus and is not centrally mediated. Local afferent sensory neurons respond to luminal distention and trigger contractions above the area of distention and relaxation below, moving the bolus forward.[3]

## ESOPHAGEAL FUNCTION TESTS

### Barium Studies of the Esophagus

A barium esophagogram, also called a barium swallow, is a radiology test with the ability to help diagnose structural lesions of the esophagus as well as to assess function. In a double-contrast esophagogram, the patient ingests an effervescent agent to distend the esophagus. Next, high-density barium is swallowed in the upright position to obtain full views of the esophagus. Structural lesions may be seen including strictures, diverticula, webs, masses, and even esophagitis. Fluoroscopic views of the patient swallowing barium boluses while prone are used to evaluate esophageal motility.[4]

Certain features identified on barium esophagogram are indicative of primary esophageal motility disorders. The classic esophagogram in achalasia shows a dilated esophagus with a "bird's beak" narrowing of the distal esophagus. In advanced cases, the esophagus may appear massively dilated or tortuous, hence called sigmoid esophagus.[5] With this classic barium study appearance and an EGD to rule out pseudoachalasia, some argue manometry studies are not needed to diagnose achalasia[4]; however, this remains controversial. A barium esophagogram performed in patients with diffuse esophageal spasm (DES) will show a classic "corkscrew" esophagus. DES manifests as repetitive nonperistaltic contractions that may obliterate the lumen. However, this classic finding is seen in less than <15 percent of patients with DES.[4]

The addition of a dynamic recording using video, called a "video fluoroscopic swallow study" or "cine-esophagogram," evaluates the pharyngeal phase of the swallow. Therefore, patients with symptoms of oropharyngeal dysphagia should have a cine-esophagogram instead of just a barium swallow.

### Esophageal Scintigraphy

Another noninvasive image-based modality used to evaluate esophageal function is esophageal scintigraphy. This nuclear medicine study uses a radiolabeled meal to evaluate esophageal transit and clearance. The study uses a gamma camera, also called a scintillation camera, to image ingested radioisotopes. Although a variety of protocols are available, the basic premise of the study includes ingestion of a technetium-99m–labeled

substance, like water, cornflakes, or applesauce, by the patient. Events are recorded at short intervals to assess bolus transport from the oropharynx to stomach. The test can be performed upright, which is more physiologic, or supine, which eliminates the force of gravity and potentially may pick up more subtle defects. The major parameter measured is total esophageal transit time, calculated from time point of entry of radioactivity into the esophagus until <10 percent of radioactivity remains in the esophagus. The test is easy to perform, quick, and usually tolerable for patients.

When the technology first emerged, many proposed esophageal scintigraphy as a useful screening test for esophageal dysmotility. One study measured esophageal scintigraphy and conventional manometry in 16 controls and 34 patients with established esophageal motility disorders.[6] An abnormal study was defined as prolonged esophageal transit greater than 15 seconds. Results were significant for lack of false negative scintigraphy results and a 96 percent agreement between conventional manometry and scintigraphy. All patients with disorders of peristalsis due to achalasia, scleroderma, and DES had an abnormal scintigraphy. Of note, only two of ten patients with esophagitis had a prolonged esophageal transit time, making scintigraphy a poor test for reflux disease.[6] In contrast to the results of some earlier studies, a more recent study found a greater number of false negatives using scintigraphy.[7] Radionuclide studies were performed on 49 patients with established esophageal dysmotility disorders and 14 controls. Although esophageal transit was prolonged in the patients with achalasia, DES, and nonspecific peristaltic disorders, only a minority of the patients with nutcracker esophagus and hypertensive LES had a prolonged esophageal transit time. This led the group to conclude that scintigraphy is useful in disorders with abnormal peristalsis but a poor study in motility disorders or cases where peristalsis is preserved.[7]

The main limitation of esophageal scintigraphy is the limited number of swallows evaluated. As some motility disorders are intermittent, they could be missed by this test. This has led some groups to advise repeat scintigraphy in those patients with a high clinical suspicion for disease.[6] Another limitation is that the presence of a hiatal hernia, particularly if a significant amount of stomach lies above the diaphragm, may be confused with distal esophagus leading to false positive results as radioactivity will persist in the hernia sac.

## Esophageal Manometry

### CONVENTIONAL ESOPHAGEAL MANOMETRY

Esophageal manometry is performed by passing a flexible catheter transnasally down the esophagus and into the stomach. Conventional esophageal manometry relies on either a multilumen water perfusion catheter (attached to a pressure transducer) or a catheter with a few discrete solid-state pressure sensors. When the information from the pressure transducers is transmitted to the computer and analyzed, continuous pressure information from the esophagus is obtained.[8] The channels on the catheter are usually spaced 3 to 5 cm apart for a total of six channels. Unfortunately, this constraint does not allow for the simultaneous recording of pressure spanning the entire esophagus including UES and LES. Therefore, the catheter has to be repositioned during the study to record from all points, starting in the stomach and slowly moving the catheter proximally, called the "pull-through" technique. Not all patients tolerate transnasal placement of the manometry catheter, and occasionally the catheters may need to be placed endoscopically.

Data from the study are displayed on a 2-D graph. The *X*-axis displays time and the *Y*-pressure on the left. There are 6 line tracings corresponding to each channel, displayed in order from least distance from nares at the top to greatest distance from nares at the bottom, the LES (Fig. 12-1).

### HIGH-RESOLUTION MANOMETRY

In the last decade, major developments in manometry technology have occurred. Newer catheters have more sensors that are closely spaced together (1 cm), which adds the ability to measure pressures within the entire esophagus, simultaneously spanning pharynx to stomach.[8] This system of monitoring pressures can allow the investigation of the full mechanics of swallow and bolus transport. Smaller segments of the esophagus not previously able to be evaluated by conventional manometry can also be analyzed.

The large volume of data acquired from the high-resolution manometry system is displayed on a 3-D color topographic map (Fig. 12-1). As in conventional manometry, the *X*-axis displays time. The *Y*-axis displays distance from nares, again with the UES at the top and LES and stomach at the bottom. Pressure is denoted by color on the *Z*-axis, with warmer colors denoting high pressure and bluer colors denoting low pressure. This topographic representation makes it easier to evaluate the full dynamics of peristalsis and bolus transport from UES to stomach.[9]

Although theoretically the high-resolution manometry system provides more data, it is unclear at this time whether it translates to greater clinical utility. However, it does appear to have a logistical benefit. The high-resolution manometry system is less operator dependent, as the pull-through technique is not needed. Furthermore, the study is now shorter for the patients and may be more tolerable. Finally, the high-resolution system may be beneficial in those challenging cases where manometric subtleties are found.

### USES OF ESOPHAGEAL MANOMETRY

As a research tool, manometry has helped clarify the intricacies of esophageal physiology. However, its clinical value is most useful when evaluating absent, weak, or abnormal peristalsis, and abnormalities in LES pressure and relaxation. With its closely spaced sensors, high-resolution manometry can also more easily define UES function and dysfunction compared with conventional manometry, as the UES only spans 1 cm in length.[9] Symptoms prompting

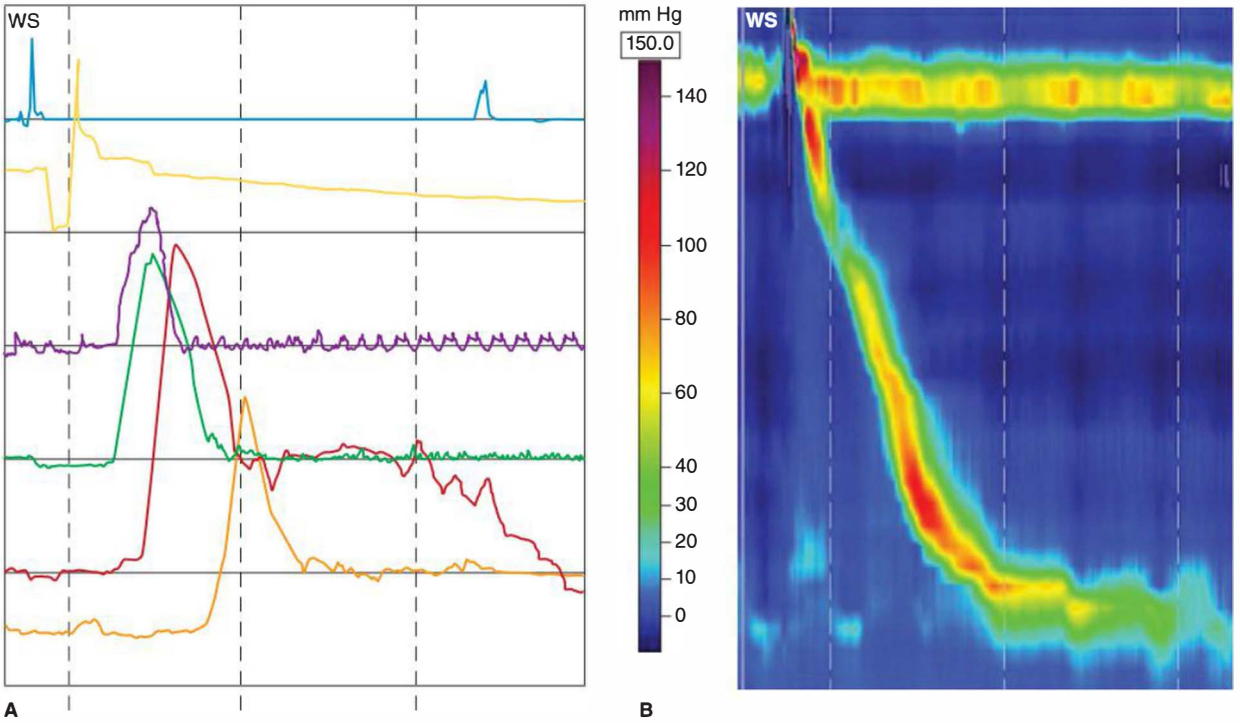



**FIGURE 12-1** Side-by-side comparison of a normal wet swallow (WS) induced peristaltic wave in conventional and high-resolution manometry. **A.** Peristaltic wave is depicted in conventional manometry as a 6-line tracing corresponding to six sensors placed in esophagus. The *X*-axis is time, and the *Y*-axis is position in esophagus. **B.** In a high-resolution manometry depiction, the *X*-axis represents time, the *Y*-axis represents position in esophagus, and *Z*-axis (color) represents pressure. Warm colors represent higher pressures.

manometry testing include dysphagia, reflux and regurgitation, and chest pain.

Mechanical causes of dysphagia such as strictures or rings are far more common than motility disorders of the esophagus. Thus, manometry usually follows radiographic and endoscopic inspection of the esophagus in the evaluation of dysphagia.[10] Unfortunately, many manometric abnormalities can be seen in asymptomatic healthy controls, and thus it is sometimes difficult to equate findings with motor disorders. However, there are certain manometric patterns of peristalsis and disordered LES function that correlate with specific disorders that lead to dysphagia. Ineffective peristalsis or complete aperistalsis on manometry can be seen in a variety of systemic disorders such as diabetes, connective tissue diseases like scleroderma, and amyloidosis. Specific patterns of peristaltic abnormalities and LES dysfunction also help diagnose primary esophageal motility disorders such as achalasia and DES.

The use of esophageal manometry for symptoms of reflux is not as straightforward. Certainly, ineffective esophageal peristalsis can be seen in patients with GERD; however, this is neither sensitive nor specific for GERD. Reduced LES pressure seen on manometry can contribute to an impaired antireflux barrier leading to GERD. However, the manometry study may be too short to pick up the TLESRs that are fundamental to the pathophysiology of GERD. Further discussion of reflux testing is described below.

Preoperative manometry for antireflux surgery is important for ruling out motility disorders in which antireflux surgery would be detrimental. Specifically, fundoplication in a patient with scleroderma, achalasia, or DES could worsen their symptoms. Postoperative manometry can be used in the evaluation of recurrent dysphagia after the fundoplication once mechanical obstruction is ruled out.

Use of preoperative manometry in prognostic determination of response to surgical treatment for GERD is more controversial. Some nonrandomized studies found that preoperative peristaltic dysfunction could lead to postoperative dysphagia with a classic 360 degree Nissen fundoplication. One group used a laparoscopic Toupet fundoplication in patients with peristaltic dysfunction on manometry and found lower rates of postoperative dysphagia compared with those with esophageal dysmotility who had a Nissen fundoplication.[11] However, a more recent randomized prospective study found no correlation between preoperative esophageal dysmotility on manometry and postoperative dysphagia in either a Nissen or a Toupet fundoplication.[12] Therefore, there is no consensus how to optimally use preoperative manometry in reflux patients.

Chest pain of esophageal origin may be due to esophageal hypersensitivity from chemical irritants, distention, or muscular contractions. Therefore, noncardiac chest pain can be due to GERD or primary motility disorders like achalasia, DES, and nutcracker esophagus. As GERD is the most

common cause of esophageal chest pain, manometry would not be a high-yield study for those limitations described above. Therefore, manometry in the evaluation of chest pain usually follows thorough investigation and treatment of GERD.[10]

Aside from diagnosis, manometry can be used in the management of some of these disorders. There are emerging data that suggest that high-resolution manometric subtypes of achalasia may have different responses to treatment, and high-resolution manometry in these patients may have prognostic information.[13] Manometry can also identify residual high GE junction pressures that may be amenable to further therapy in those patients with recurrent dysphagia following endoscopic or surgical therapy for achalasia.

## Esophageal Reflux Testing

### CATHETER-BASED pH TESTING

Ambulatory pH monitoring is used for diagnosis of GERD, evaluation of treatment failure, and preoperative evaluation. The test involves placement of a transnasal catheter 5 cm above the LES. Patients are instructed to continue daily activities and diet. A 24-hour test will record pH events, with acid reflux events defined as a pH <4.0 for 5 or more seconds. Patients also employ event buttons to record meals, postural changes, and symptoms. The most important recorded measurements include percentage of time when pH <4, percent of upright time when pH <4, percent of supine time when pH <4, number of reflux episodes, number of reflux episodes >5 minutes, and the longest reflux episode. Using these six parameters, the DeMeester score is calculated to estimate global acid exposure. The sensitivity and specificity of ambulatory pH catheter testing for GERD reach 77 to 100 percent and 85 to 100 percent, respectively, in patients with endoscopically proven esophagitis. However, the sensitivity of pH testing ranges from 0 to 71 percent in endoscopy-negative reflux disease (NERD).[14]

### WIRELESS CAPSULE pH TESTING

Now available is a wireless pH recording capsule, the Bravo system (Medtronic, Minneapolis, MN, USA). This system was devised to avoid the limitation of patient intolerance of the transnasal catheter pH testing. The capsule is attached to the esophageal mucosa using a flexible introducer, positioned 6 cm above the GE junction as determined by endoscopy or esophageal manometry. pH data are recorded onto an external receiver by radio telemetry. The wireless system is equivalent to the catheter-based system in recording accurate pH data.[15] The capsule naturally falls off several days after placement. The advantage of the wireless system is better patient tolerability. Patients are more likely to go about their normal routines including diet and exertion, which may avoid false negative results. Furthermore, increased tolerability may translate to extension of study time. Forty-eight hours of data increase the diagnostic accuracy for GERD. Disadvantages include greater cost of the test and the rare risk of chest pain requiring endoscopic removal of the capsule.[14]

### IMPEDANCE TESTING

Broadly defined, GERD is the exposure of the esophagus to gastric contents causing symptoms. Wireless and catheter-based ambulatory pH monitoring can measure the acidity of the refluxate but does not evaluate weakly acidic or non-acidic reflux events, which may still cause symptoms. Thus, a system was devised to detect all types of liquid movement in the esophagus using intraluminal electrical impedance. Intraluminal impedance monitoring uses a cylindrical catheter-containing multiple metallic electrodes. It is passed transnasally and swallowed by the patient to be placed within the esophagus above the GE junction.

The principle behind measurement of impedance is that the current flow between two electrodes will depend upon the conductivity of the surrounding environment. A liquid bolus has high electrical conductivity, and thus the resistance (or impedance) between the two electrodes will drop. On the other hand, an air bolus has low conductivity and impedance will increase. The sequence of impendence changes between the different segments of electrodes can establish directionality to determine whether the flow is related to swallowed material or esophageal reflux.[16]

Impedance is measured with at least three electrodes spaced 2 cm apart. The placement of the most distal electrode should be 1 to 2 cm above the LES. A number of studies have evaluated gas, liquid, and acid reflux in animals, asymptomatic controls, and patients with reflux using impedance monitoring compared with fluoroscopic exam, manometry, and pH monitoring. The sensitivity for detecting reflux using impedance ranged from 92 to 99 percent.[16–18] Therefore, the technical recommendations from a workshop led by 11 GERD specialists advise that appropriate electrode placement should detect at least 90 percent of reflux events.[16] Sensitivity may be affected by conditions that lead to low baseline impedance values. Esophagitis and Barrett's esophagus (BE) are two such conditions; therefore, it is important to be aware of these entities prior to analysis of impedance studies.

Impedance monitoring is often combined with pH monitoring to increase diagnostic accuracy and determine the specific type of reflux causing symptoms. One study measured pH and impedance events in 60 patients with heartburn or regurgitation and established the statistical relationship between symptoms and reflux events. The combination of impedance and pH yielded a higher proportion of patients with a positive symptom association probability (SAP) compared with either test alone.[19]

### USES OF pH MONITORING

Whether to perform pH monitoring on or off proton pump inhibitor (PPI) therapy is debated, but it primarily depends on the purpose of the study. If the purpose is to define

whether the patient's symptoms are stemming from GERD as opposed to another etiology, ambulatory pH monitoring should be performed off PPI therapy. Should the patient continue taking PPIs in this case, the study may be falsely negative. If the purpose of the study is to define whether PPI therapy is effectively reducing acid exposure in patients with known GERD, the study would be useful with continuation of PPI therapy.

### BILITEC

Another element of symptomatic reflux disease may stem from reflux of duodenal contents into the esophagus, hence called "Duodenogastroesophageal reflux disease" (DGER). The Bilitec 2000 (Synectics Medical, Enfield, UK) monitoring system uses measurement of bilirubin concentration as a marker for duodenogastric reflux. The probe that is inserted transnasally into the esophagus is a fiber optic spectrophotometer that can identify presence of bile. Recording takes place over a 24-hour period.[20] There are several limitations to the Bilitec system. Notably, the sampling rate is once per 8 seconds; therefore, it is unlikely to accurately evaluate timing of DGER events. In addition, solid material may become trapped in the sensor at the probe tip, impairing accurate measurement and increasing artifact.[16] Thus, testing is most accurate when patients are on a liquid diet, but unfortunately this does not reproduce normal physiologic settings. Despite its limitations, the Bilitec system is the only system that evaluates the presence of bile in reflux events.

## ENDOSCOPIC TECHNIQUES

### Endoscopic Imaging

#### HIGH-RESOLUTION AND HIGH-MAGNIFICATION ENDOSCOPY

Endoscopy is used to visually inspect esophageal mucosa and may be used to inspect dysplastic or malignant tissue. The image quality depends upon magnification and resolution. Resolution is the ability to distinguish two closely spaced pixels and is expressed as pixel density. Standard endoscopes carry chips that capture images with a resolution of 640 to 700 pixels wide × 480 to 525 pixels high.

There are three high-resolution endoscope systems available in the United States. The chips in these systems capture images with resolutions of 1280 × 1024 and 1280 × 960, over a million pixels. These high-resolution endoscopes must be used with a high-definition compatible system including processor and monitor. A standard endoscope displays an image that is magnified 30 to 35 times. High-magnification endoscopes use a combination of digital and optical zoom to magnify up to 150 times.[21]

Higher resolution and magnification improves the quality of the image captured and displayed (Fig. 12-2). Theoretically, this increases the detection of abnormal esophageal tissue like BE or malignancy. However, the majority of studies of high-resolution or magnification endoscopy are also comparing other techniques that are discussed below.




**FIGURE 12-2** High-resolution endoscopy image of abnormal BE mucosa.

#### CHROMOENDOSCOPY

Chromoendoscopy refers to the application of stains or dyes via spray catheter to the gastrointestinal mucosa at the time of endoscopy. Stains available include Lugol's solution, methylene blue, toluidine blue, and crystal violet, classified as absorptive stains. These stains preferentially absorb in specific cells, allowing for distinction of cell types. Indigo carmine is a contrast dye that absorbs in mucosal defects and can thus identify mucosal irregularities. Finally, reactive dyes such as congo red chemically react under certain conditions like low pH. Acetic acid is an agent that can be sprayed topically during endoscopy but does not dye the mucosa and thus is not technically considered chromoendoscopy. However, it temporarily denatures glycoproteins in the mucosa and will help detect dysplastic or abnormal tissue.[22] The major limitation of chromoendoscopy is that it increases procedure time. A high interobserver variability also limits this technique.

Chromoendoscopy can be used throughout the GI tract to detect inflammatory, dysplastic, or neoplastic tissue. In the colon, it is predominantly used for dysplasia surveillance in inflammatory bowel disease. In the esophagus, chromoendoscopy is predominantly used for detection of dysplasia in BE or early cancer, either adenocarcinoma or squamous cell carcinoma.

In methylene blue chromoendoscopy, normal epithelial cells absorb the dye while dysplastic or malignant cells do not. Although several studies showed an increase in diagnostic yield to detect dysplasia in BE using methylene blue as compared with random biopsies, a recent meta-analysis of nine studies failed to show a significant increase in diagnostic yield. However, this result may be an effect of

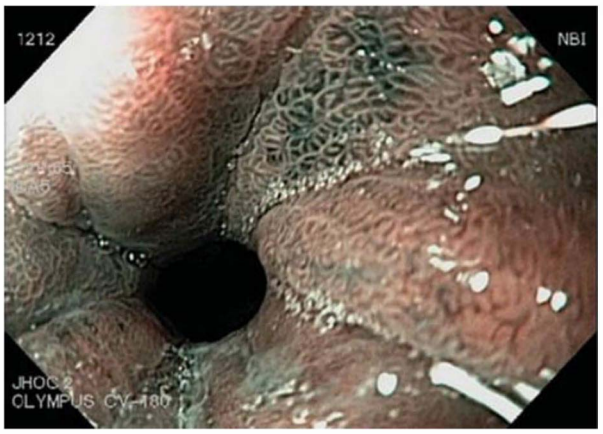



**FIGURE 12-3** Narrow-band imaging of BE mucosa.

differences in inclusion criteria and application techniques in various studies.[23]

## NARROW-BAND IMAGING

A digital-based technique to enhance the contrast of mucosal changes may overcome these limitations. To illuminate mucosa, standard endoscopy uses a white light that passes through a rotary RGB filter to separate wavelengths corresponding to red, green, and blue. Narrow-band imaging (NBI) uses a filter with a narrower range that predominantly allows blue (415 nm) and green (540) wavelengths to pass, while blocking red (650 nm) wavelengths.[24] Given that longer wavelengths of light penetrate deeper layers of mucosa, the shorter blue and green wavelengths enhance the contrast of the superficial mucosa (Fig. 12-3). As hemoglobin absorbs blue light, NBI is also particularly helpful in assessing microvasculature of the GI mucosa. The narrow-band filter can be switched on and off by the endoscopist, facilitating ease of use with standard white light endoscopy.

As in chromoendoscopy, NBI can be used throughout the GI tract, particularly for detection of early gastric cancer and colonic polyps or dysplasia. In the esophagus, NBI has most been studied in BE. Several classification systems have been devised to characterize NBI findings in BE. One group simplified a classification system into A to D. Grade A was characterized by round pits with regular microvasculature; grade B, villous/ridge pits with regular microvasculature; grade C, absent pits with regular microvasculature; and grade D, distorted pits with irregular microvasculature. This classification was validated in a study where grade A had a high predictive value for columnar mucosa without BE, grades B and C were predictive for nondysplastic BE, and grade D predicted BE with high-grade dysplasia. Low-grade dysplasia could not easily be distinguished from nondysplastic without dysplasia.[25]

Detection of high-grade dysplasia is important for determining management of BE. Current surveillance guidelines use random four quadrant biopsies every 1 or 2 cm of BE for dysplasia detection, but they may be suboptimal. A recent meta-analysis of eight studies with close to 500 patients examined the accuracy of NBI in detection of high-grade dysplasia with histological confirmation. The pooled sensitivity and specificity was 96 and 94 percent, leading the authors to conclude that NBI has a high diagnostic accuracy for detection of high-grade dysplasia.[25]

Few studies have directly compared NBI with chromoendoscopy to determine which, aside from endoscopist preference, would be more beneficial in detection of dysplasia. The only randomized prospective study included 28 patients with known Barrett's and high-grade dysplasia or early esophageal cancer. Each patient was randomized to high-resolution endoscopy with adjunct NBI or high-resolution endoscopy with adjunct chromoendoscopy. Six to eight weeks later the patients crossed over to the other modality performed by a separate endoscopist. Although the majority of high-risk lesions were detected on high-resolution endoscopy alone, both NBI and chromoendoscopy picked up several additional lesions equally well.[26]

## CONFOCAL ENDOMICROSCOPY

Confocal laser endomicroscopy (CLE) is a tool that enables gastroenterologists to obtain real-time in vivo histology at the time of endoscopy. In CLE, tissue is illuminated with a low-power laser. The laser light is reflected back and focused through the same lens, the size of a pinhole. The images obtained have a high enough resolution (up to 1000×) that histologic information is available (Fig. 12-4). This technique requires administration of an intravenous or topical fluorescence agent. The most commonly used agent is intravenous fluorescein sodium, which is a renally excreted agent that is distributed within 7 to 14 seconds across the vasculature to GI tissue. Various topical sprays that stain either nuclei or cellular cytoplasm may be used as well.[27]

CLE is available in a probe-based system or an integrated endoscopic system. In the latter, the confocal microscope is integrated into the distal end of a white light endoscope. Images from the integrated scope are displayed on two monitors, concomitantly showing both video and endomicroscopy views. Probe-based CLE systems use a stand-alone confocal probe that can pass through the accessory channel of a standard endoscope.[27]

CLE has been used to classify colon polyps, determine diagnosis of or direct celiac disease biopsies, detect early gastric cancer, or *Helicobacter pylori* infection. In the esophagus, CLE is useful in detection of BE and early neoplasia. As in NBI and chromoendoscopy techniques, CLE can distinguish BE from early neoplasia. Confocal endomicroscopy features of high-grade dysplasia include irregular cells with loss of normal cellular pattern, distorted subepithelial capillaries, and leakage of fluorescein.

A clinically relevant outcome using CLE technology is that fewer mucosal biopsies may be needed to detect

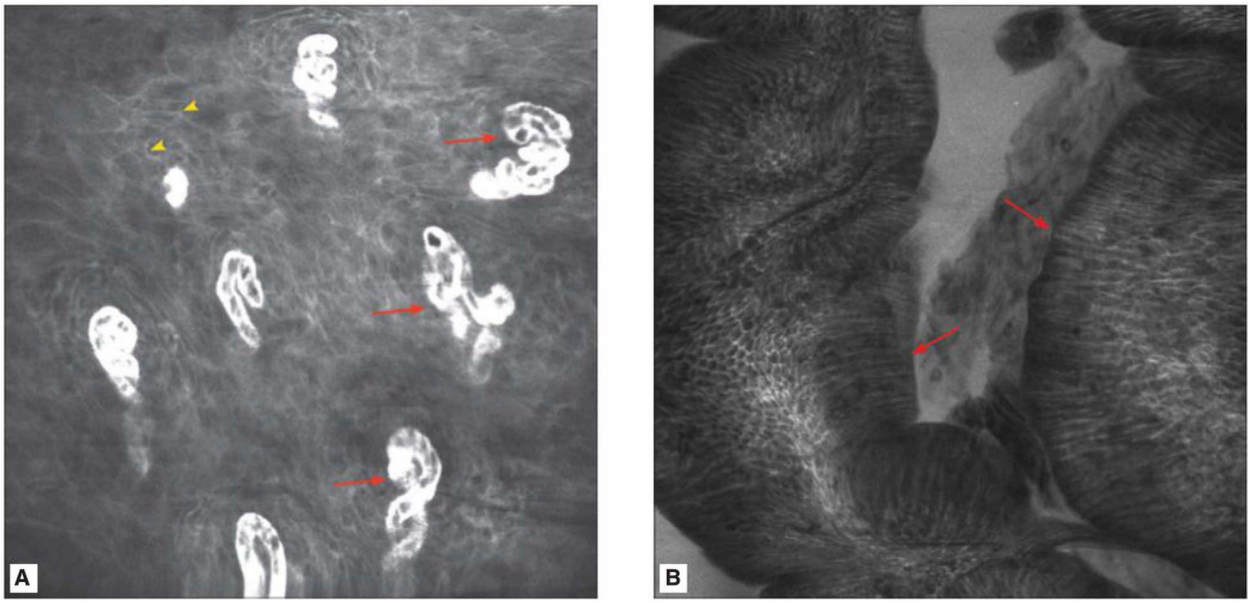



**FIGURE 12-4** Confocal endomicroscopy images of esophagus. Image **A** shows confocal endomicroscopy image of the squamous esophagus (1000× magnification). The arrows point to intrapapillary capillary loops. Arrowheads point to the intracellular spaces between epithelial cells. Image **B** shows an image of Barrett's esophagus. The arrows point to the cells in a villiform, glandular pattern.

high-grade dysplasia or early neoplasia. One study randomized 39 patients to standard endoscopy with four-quadrant random biopsies or CLE with four-quadrant optical biopsies as well as targeted biopsies. Several weeks later, the patients were crossed over. The diagnostic yield for high-grade dysplasia or cancer was higher in the confocal endomicroscopy procedures. In those 16 patients who were considered high risk, with suspected but unlocalized neoplasia, there was an almost 60 percent reduction in the number of biopsies needed to obtain the diagnosis. In the remaining 23 patients who were undergoing routine BE surveillance, 65 percent did not require any mucosal biopsies based on confocal images, and no neoplasia was identified.[28]

## ENDOSCOPIC ULTRASOUND AND FINE-NEEDLE ASPIRATION

Endoscopic ultrasound (EUS) adds high-frequency sonographic information via an ultrasound transducer at the tip of the endoscope to provide imaging of the GI wall and surrounding structures. Echoendoscopes are available in three types of designs: radial array, curvilinear array, and probe based. Radial array echoendoscopes provide a 270- to 360-degree view of the surrounding structures whereas curvilinear echoendoscopes provide a 180-degree view parallel to the scope. Some systems have Doppler capabilities to visualize blood vessels.

The curvilinear echoendoscope is ideal for fine-needle aspiration (FNA). The needle, passed through the accessory channel, will be seen in the plane of the ultrasound, allowing for accurate and safe biopsies or other therapies. Needles available range from 19 to 25 gage and can penetrate up to a depth of 10 cm. The risks of EUS without FNA are equal to that of standard endoscopy. Although still quite low at 1 percent, EUS–FNA has a slightly greater risk than EUS without FNA.[29] Notably, risk of infection during aspiration of cystic lesions is higher, and antibiotic prophylaxis is warranted.

EUS can be used for diagnosis and management of luminal GI, pancreatic, or biliary disorders. In the esophagus, EUS produces images corresponding to the five histologic layers of the GI tract. The endosonographic images appear as alternating hyper and hypoechoic bands. The innermost band is hyperechoic and corresponds to the lumen or superficial mucosal layer. The second layer corresponds to the lamina propria, the third corresponds to the submucosa, the fourth corresponds to the muscularis propria, and the fifth corresponds to the adventitia. Beyond the adventitia, adjacent structures such as lymph nodes can be visualized (Fig. 12-5). This makes EUS suitable for evaluation of submucosal lesions and staging esophageal cancer.

Locoregional TNM staging is vital in determination of surgical or medical management of esophageal carcinoma. EUS has a greater diagnostic accuracy for staging compared with computed tomographic (CT) scanning.[30] Furthermore, using cost-effectiveness analysis models, EUS may be more cost effective than other strategies by detection of celiac lymph nodes that would prevent unnecessary surgery.[31]

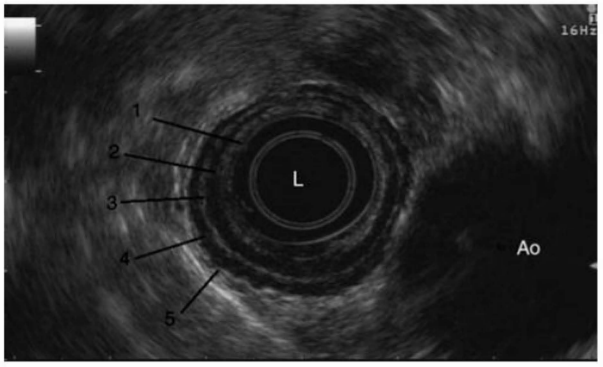



**FIGURE 12-5** Radial EUS visualization of layers of the esophagus and adjacent structures. 1, luminal fluid and mucosal surface interface, 2, mucosa, 3, submucosa, 4, muscularis propria, 5, adventitia. Ao, aorta; L, esophageal lumen.

## Therapeutic Procedures

### ENDOSCOPIC MUCOSAL RESECTION

Advanced endoscopic therapies may obviate the need for surgery in certain cases. Endoscopic mucosal resection (EMR) is one such therapy that pertains to esophageal pathology, particularly in BE with dysplasia and very early esophageal cancers that have not extended into the submucosa. Although a variety of techniques have been described, the two major methods include EMR with a cap (EMRC) or EMR with ligation (EMRL). The first step to mucosal resection includes injection of a substance, usually normal saline with or without epinephrine, to lift the lesion in question off the muscularis propria. Other solutions like hypertonic saline, 10 percent glycerol/5 percent fructose, 50 percent dextrose, and sodium hyaluronate have also been used.[32]

EMRC uses a transparent cap fitted to the endoscope. Once the lesion has been lifted, a snare is passed through the accessory channel and opened inside the cap. The lesion is then suctioned into the cap where it can be excised with the snare. EMRL uses a single-band or multiband ligation device similar to those used for treating esophageal varices. The band ligator is deployed, grasping the lesion into a polypoid configuration. This allows for resection via snare and retrieval (Fig. 12-6).

The risks of EMR include perforation, bleeding, and stricture formation with large areas of EMR. It appears that EMRC and EMRL have similar safety profiles. Despite these adverse risks, EMR is generally safe in experienced hands and can be done in an outpatient setting.

Esophageal indications for EMR include early esophageal cancer and BE with dysplasia. Accepted criteria for EMR as proposed by the Japanese Society for Gastroenterological Endoscopy (JSGE) include esophageal cancer lesions less than 2 cm in diameter and involvement of less than 1/3 of the esophageal circumference. EMR for lesions extending into the submucosa is contraindicated, and thus relevant investigations like EUS can be considered prior to EMR.

Traditionally, patients with high-grade dysplasia in BE were offered esophagectomy, especially in light of possible concomitant carcinoma. However, now with ablative techniques such as EMR, patients may be offered endoscopic therapy instead. One study found a curative rate of 96.6 percent when treating 279 patients with either high-grade dysplasia

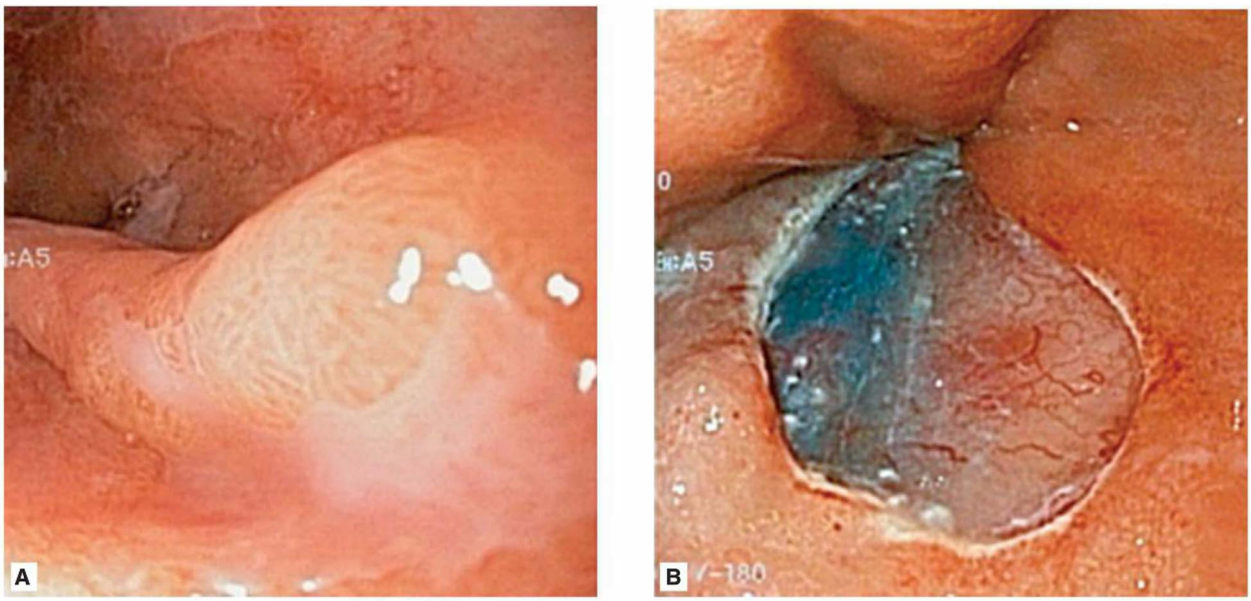



**FIGURE 12-6** **A.** BE with nodule **B.** After endoscopic mucosal resection and submucosal injection of indigo carmine.

($N = 61$) or early neoplasia. Patients required an average of two EMR sessions to achieve complete response. Risk factors associated with local recurrence included piecemeal resection, long-segment BE, lack of post-EMR ablative therapy (see the sections below), time to complete response greater than 10 months, and multifocal neoplasia.[33]

## PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is another ablative technique for BE and early esophageal cancer. PDT can be used alone or may follow EMR to ablate residual dysplastic tissue after resection of focal lesions. The principle behind PDT is that when exposed to intense light, certain photosensitizing chemicals produce oxygen and other radical species. These radical species cause nonthermal cellular necrosis and vascular thrombosis. The only systemic photosensitizer approved by the FDA is porfimer sodium. It is given as an intravenous infusion over 3 to 5 minutes. Porfimer sodium is absorbed by most tissues but is selectively retained in neoplastic tissue. After approximately 48 hours, the photosensitizer is only retained in neoplastic tissue and has cleared normal tissue. Thus, PDT endoscopic therapy is usually scheduled 48 hours after infusion.

Porfimer sodium becomes activated in response to light at 515 and 630 nm wavelengths. Therefore, a specific light source has to be used at endoscopy, in contrast to standard white light endoscopy. The FDA-approved 630 nm red light source that is available also contains an automatic feature to change power and duration of treatment based on indication of procedure (e.g., BE vs. carcinoma). A variety of catheters and balloon catheters are available to deliver light to pretreated tissue in a circumferential fashion. Treatment is delivered for 8 to 12 minutes depending on indication.[34]

The major risk of PDT is stricture formation. Risk factors for this complication include long-segment BE, multiple PDT treatments, preceding EMR, history of chemoradiation, and history of prior stricture. As some residual photosensitizer remains in the patient's skin for up to 30 days, they are advised to avoid direct sunlight as severe sunburns can result.

## RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) is another technique used in BE and other conditions. RFA can be performed circumferentially or focally. Circumferential RFA in the esophagus uses a 3-cm balloon ablation catheter in which resides a coiled electrode array. Two pulses of electric current at an energy level of 10 to 12 J/cm$^2$ are sufficient for ablation of full-thickness epithelium, without damaging the submucosa. Prior to placement of the balloon catheter, the esophageal luminal diameter has to be measured. The balloon ablation catheter's outer diameter must not be greater than the esophageal luminal diameter. The balloon ablation catheter is introduced via guidewire, followed by the endoscope.

Focal RFA is usually performed after circumferential ablation, if residual Barrett's tissue remains or when small amounts of BE are present. Instead of a balloon ablation catheter, focal RFA uses an electrode array that is mounted at the tip of the endoscope and seen in the 12 o'clock position.

As in EMR and PDT, RFA can be used for BE with high-grade dysplasia. However, it also has a role in low-grade dysplasia to prevent progression to high-grade dysplasia and cancer. Although more controversial, RFA can also be used in BE without dysplasia. Recently published was the longest running study, AIM-II, which followed 50 patients who had RFA of nondysplastic BE. At 2.5 years, 98.4 percent of patients had complete eradication of all metaplastic tissue. At 5 years, 92 percent still had complete eradication, while the remaining patients obtained complete eradication with further treatment with focal RFA.[35] Complications of RFA include bleeding, strictures, and postprocedure pain.

## CRYOTHERAPY

Cryotherapy is a nonthermal noncontact ablative technique that, when applied via endoscopy, causes freezing of the mucosa and induction of necrosis. The technology is based on the Joule–Thomson effect that dictates that the temperature of a liquid gas will drop when the surrounding pressure drops. There are currently two cryoablation systems available, one based on liquid nitrogen and the other on carbon dioxide. The cryoablation system includes a pressurized canister of compressed gas or liquid nitrogen. This cryospray is delivered to esophageal tissue via a single-use side or end-firing catheter that passes through the standard endoscope accessory channel. Once the gas is released from the tip of the catheter, tissues sprayed freeze in the context of decreased pressure. A suction tube is affixed to the tip of the endoscope or passed separately next to the scope to simultaneously remove evacuated gas that would distend the GI tract. Each application lasts 10 to 20 seconds and multiple applications can be performed to one area, with 10 to 30 seconds in between each to allow for thawing.

Cryotherapy can ablate tissues throughout the GI tract and has been studied in gastric antral vascular ectasia (GAVE) and radiation proctopathy. In the esophagus, cryotherapy is another ablative technique for BE and early carcinoma. Early data for cryotherapy suggest that it can eradicate high-grade dysplasia in a high proportion of patients.[36]

## ENDOSCOPIC SUBMUCOSAL DISSECTION

Endoscopic submucosal dissection (ESD) is a technique used to remove esophageal lesions that are flat and greater than 2 cm. This provides the pathologist the opportunity to examine the tissue en bloc. The lesion is not removed via a modified "polypectomy" as in the EMR technique. The initial step of ESD involves marking the margins with electrocautery. Next, the lesion is lifted with submucosal injection as described in the EMR section. An incision is then made in a circumferential manner with a special endoscopic electrocautery knife. A variety of electrocautery knives have been

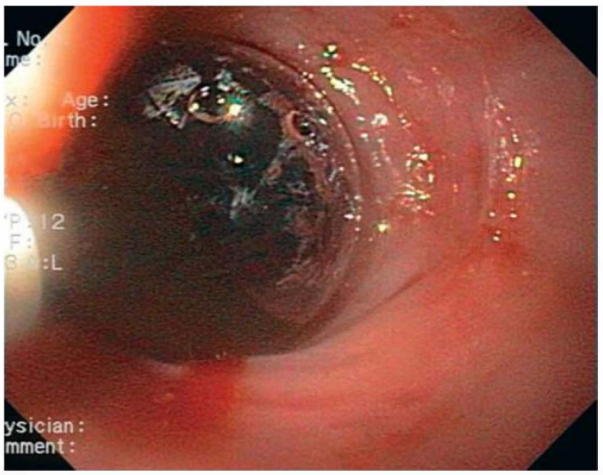



**FIGURE 12-7** Through the scope (TTS) balloon dilation o f esophageal stricture.

developed for use. Once the lesion is dissected off the deeper layers, it can be removed en bloc.

ESD can be a time-consuming procedure, lasting over an hour for one lesion. Complications include acute or delayed bleeding, perforation, and stricture. Perforation rates for ESD are higher than those of EMR.[37] The most experience with ESD comes from resection of early gastric cancer in Asia. However, ESD can be applied to high-grade dysplasia or early esophageal cancer as well.

## ESOPHAGEAL DILATION

Esophageal dilation can be used to manage benign and malignant esophageal strictures, postsurgical anastomotic strictures and is a mainstay of therapy for achalasia. There are two basic kinds of esophageal dilators: balloon-based dilators and mechanical (Bougie) dilators. Balloon dilators are typically passed through the scope and through the stricture (Fig. 12-7). For narrow strictures, wire-guided balloons are available. There are several types of mechanical dilators, such as Maloney dilators, which are not wire-guided, and Savary dilators that are wire-guided. Fluoroscopy is helpful for guiding dilation of difficult or proximal esophageal strictures. Balloon dilators disrupt strictures by exertion of radial force, while mechanical dilators exert force radially and longitudinally. Potential complications of esophageal dilation include esophageal perforation and bleeding. The "rule of threes" for esophageal dilation suggests that no more than three dilators of increasing size should be used in each dilation session, which allows increasing the lumen of the stricture by about 3 mm.[38]

With mechanical dilators, the amount of resistance of a stricture can be felt by the endoscopist passing the dilator, which also helps guide therapy. Achalasia dilation is performed with 30- to 40-mm pneumatic balloons, typically with fluoroscopic guidance. Symptomatic improvement in dysphagia is as high as 85 percent, but dysphagia returns in one-third to half of patients.[39] Complications of dilation can include bleeding and esophageal perforation, with rates of 0.1 percent for simple dilations and 3 percent for large pneumatic dilations.[40]

## ESOPHAGEAL STENTS

Esophageal stents are used to maintain the lumen in a variety of benign and malignant conditions. Stents are either self-expanding metal stents (SEMS) or self-expanding plastic stents (SEPS). SEMS are composed of woven metal meshes that expand to exert radial force until the maximum diameter is reached. Multiple sizes and diameters are available. Certain metals are more flexible and are thus more appropriate for stenting across angulations. SEMS have flares on one end to prevent migration. SEMS can be wholly or partially covered with a polymer membrane to prevent tumor infiltration. This allows for future repositioning or removal. In contrast, ingrowth of tissue prevents the ability of uncovered SEMS to be removed or repositioned.

SEPS are completely covered with a silicone membrane to prevent tissue ingrowth. They were designed to facilitate ease of repositioning and removal. However, SEPS have high rates of migration and may not have long-term clinical efficacy for malignant conditions. Decision to use a SEPS as opposed to a covered SEMS has to be carefully made.

Esophageal stents are deployed over a guidewire, generally with fluoroscopic guidance. Esophageal lumens less than 12 mm require dilation prior to successful placement of SEMS. Complications of esophageal stent placement include bleeding and perforation. Particularly with bulky upper esophageal tumors, airway compression as the stent expands can be life threatening and simultaneous bronchoscopy with tracheal stent placement should be considered. Another complication of stent placement is pressure necrosis with subsequent fistula formation.

Indications for esophageal stenting includes palliation for unresectable esophageal cancer. Dysphagia may be relieved in a high proportion of patients, improving quality of life. Esophageal stents have also been used in benign esophagotracheal fistulas, anastomotic leaks, or perforations. Although results have been favorable in multiple case series and observational studies for these conditions, there are no randomized control trials comparing stents to surgical therapy. Esophageal stents for benign esophageal stricture are used occasionally, but much less frequently than in malignant disease and with careful patient selection.[41]

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## ESOPHAGEAL PHYSIOLOGY, FUNCTION TESTS, AND ENDOSCOPIC TECHNIQUES BOARD REVIEW QUESTIONS (CHAPTER 12)

1. Which of the following contribute to the lower esophageal sphincter pressure?
   A. Circular smooth muscle of the distal esophagus alone
   B. Longitudinal smooth muscle of the distal esophagus alone
   C. Striated muscle of the right crus of the diaphragm alone
   D. Circular and longitudinal smooth muscle of the distal esophagus
   E. Circular smooth muscle of the distal esophagus and striated muscle of the right crus of the diaphragm

2. A 47-year-old female presents with a 5-year history of substernal burning. Proton pump inhibitor (PPI) therapy is ineffective and upper endoscopy is unremarkable. A 24-hour pH study demonstrates 12 reflux events. Four of these events were associated with symptoms. What is the next appropriate step in management?
   A. Increase PPI regimen
   B. Surgical referral for fundoplication
   C. Initiate antidepressant therapy
   D. Perform esophageal manometry
   E. Perform esophageal scintigraphy

3. A 72-year-old man with newly diagnosed adenocarcinoma of the esophagus presents for evaluation. What is the most sensitive test for locoregional staging of his cancer?

   A. CT scan
   B. PET scan
   C. Endoscopic ultrasound
   D. Barium esophagogram
   E. Chromoendoscopy

4. A 20-year-old male presents with chest pain associated with eating. His upper endoscopy is normal. Which is the next most appropriate test?

   A. Esophageal manometry
   B. Barium esophagogram
   C. CT scan of chest
   D. 24-hour pH test
   E. Capsule endoscopy

5. A 64-year-old man is found to have early adenocarcinoma on endoscopic surveillance for Barrett's esophagus. Which is of the following is not an acceptable form of management?

   A. Esophagectomy
   B. Endoscopic mucosal resection of lesion followed by photodynamic therapy
   C. Endoscopic mucosal dissection of lesion
   D. Cryotherapy
   E. Continued endoscopic surveillance every 6 to 12 months

## ANSWERS

1. **Answer: E.** A combination of the circular smooth muscle of the distal esophagus and striated muscle of the right crus of the diaphragm comprises the lower esophageal sphincter.
2. **Answer: C.** A 24-hour pH testing is quite sensitive and specific and the patient's symptoms do not correlate with significant reflux. Further testing with manometry and scintigraphy is not warranted.
3. **Answer: C.** Endoscopic ultrasound will provide staging for tumor size and lymph nodes. Barium esophagography and chromoendoscopy do not provide staging information. CT and PET scanning are useful for regional as well as distant disease, but cannot provide detail on depth of local tumor invasion.
4. **Answer: D.** The most likely diagnosis is gastroesophageal reflux, and 24-hour pH testing is the appropriate study.
5. **Answer: E.** This patient has established and documented malignancy and needs some form of resectional or ablative therapy. Continued surveillance without initiation of treatment is inappropriate.

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# 13 Congenital Esophageal Anomalies

*Nishant D. Patel*
*Avedis Meneshian*

**KEY CONCEPTS**

- Epidemiology
  - Esophageal atresia and tracheoesophageal fistula (EA–TEF) occurs in 1 in 3400. Esophageal duplication cysts represent 10 to 15 percent of foregut duplication cysts and 5 to 10 percent of mediastinal cysts. The true incidence of esophageal duplication cysts is unknown. Congenital esophageal stenosis and webs occur in 1 in 25,000 to 50,000 live births.
- Classification
  - Anatomic variations of EA–TEF include isolated EA, EA with distal TEF, EA with proximal TEF, EA with distal and proximal TEF, or N-type TEF. EA with distal TEF is the most common. Esophageal duplication cysts can be cervical, thoracic, or abdominal. Esophageal stenosis and webs can be characterized on the basis of etiology into fibromuscular thickening, trachobronchial remnants, and membranous web.
- Clinical features
  - EA–TEF is suggested by polyhydramnios, and infants present with drooling, rhonchi, aspiration with subsequent respiratory distress. Esophageal duplication cysts are often asymptomatic. Symptoms due to esophageal duplication cysts are secondary to mass effect and include dysphagia and respiratory insufficiency. Congenital esophageal stenosis and webs present in infancy with dysphagia and vomiting of solid food.
- Diagnosis
  - EA–TEF is readily diagnosed with passage of a 10-F esophageal tube and gentle insufflation, and plain chest radiograph. The presence of air in the stomach confirms a distal TEF, and its absence suggests isolated EA. Esophageal duplication cysts are also diagnosed on plain film and confirmed with esophagography and CT. Esophageal stenosis and web are diagnosed with esophagography and endoscopy.
- Treatment
  - Surgical repair of EA–TEF consists of a single-layer primary anastomosis of the proximal and distal esophageal segments and ligation of any TEF. Esophageal duplication cysts are resected. Esophageal stenosis and webs are initially managed conservatively with dilatation. Surgical treatment is reserved for stenosis refractory to dilatation and consists of resection of the stenotic segment and primary anastomosis.
- Complications
  - Outcomes following repair of EA–TEF are good. Early complications include anastomotic leak and subsequent sepsis. Mid-to-late-term complications include stricture, recurrent fistula, and gastroesophageal reflux.

## ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA

### Epidemiology

The incidence of esophageal atresia (EA), with or without tracheoesophageal fistula (TEF), is approximately 1 in 3400.[1] There is a reported slight preponderance in males and children of diabetic or older mothers.[2] Chromosomal anomalies have been reported in 6 to 10 percent of cases.[3] Although EA–TEF can be an isolated finding, epidemiologic studies suggest that up to 60 percent will have other anomalies.[2] Some will present with other anomalies that lead to a specific genetic diagnosis, whereas others will present with a nonrandom association of other defects. These other defects include coloboma, heart, atresia choanae, retarded development,

genital hypoplasia, and ear abnormalities (CHARGE associations), as well as vertebral, anal, cardiac, tracheoesophageal fistula, renal, and limb defects (VACTERL).

## Embryology

EA constitutes a spectrum of incomplete esophageal development, which arises from interruptions in endoderm–mesoderm interactions. Although the exact embryologic mechanism of EA–TEF is not well characterized, some of the mechanisms have been recently discovered. Most studies on EA–TEF have used intraperitoneal Adriamycin injections in pregnant rodents, which reproduces the VACTERL association that is identical to the defects found in humans.[4] In this model, the esophagotracheal foregut tube fails to divide into ventral and dorsal parts, and a fistula develops. Several molecular pathways seem to play an important role. Some studies have shown that when genes for the retinoic acid receptors were deleted in mice, the foregut tube failed to separate.[5] The hedgehog signaling pathway has also been implicated.[6] Targeted deletion of the sonic hedgehog gene resulted in mice embryos with severe TEF malformations.[6] The Hox genes are thought to play a role in endodermal patterning and are expressed in the endodermal and mesodermal germ layers. Mice that are null mutant for Hoxc4 develop a partially or completely blocked esophageal lumen.[7] In another study, T-box transcription factor 4 misexpression resulted in failure of tracheoesophageal septum formation in chicks.[8,9] Despite these studies, the exact pathogenic mechanism behind EA–TEF remains elusive.

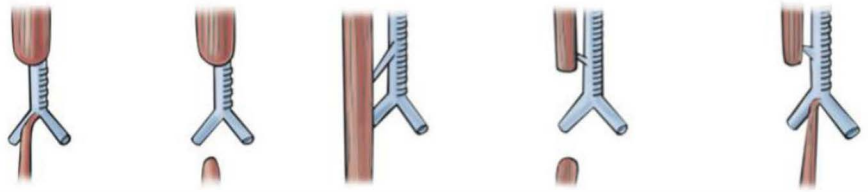
## Classification, Clinical Presentation, and Diagnosis

EA is characterized using the Ladd[10] or Gross[11] classification system. In general, the different variants include isolated EA, EA with distal TEF, EA with proximal TEF, EA with proximal and distal TEF, and N-type TEF. EA with distal TEF (gross class C or Ladd III/IV) is the most common EA anomaly, seen in approximately 87 percent (Table 13-1). Infants with N-type EA and those weighing less than 2000 g are more likely to present with associated anomalies.[12] The most common associated anomalies are cardiovascular malformations, seen in up to 30 percent infants with EA.[13] These include atrial and ventricular septal defects, patent ductus arteriosus, tetralogy of Fallot, and anomalies of the aortic arch.

The diagnosis of EA–TEF is usually made in the first 24 hours of life, but can be made antenatally or delayed.[14,15] Prenatal ultrasound detects EA by the presence of polyhydramnios (amniotic fluid index >97.5 percentile) with a small or absent stomach.[16] Polyhydramnios occurs because of the fetus' inability to swallow amniotic fluid. If an EA is detected on ultrasound without polyhydramnios, a distal TEF allows the amniotic fluid to pass into the stomach.

In early postnatal life, infants with EA–TEF will accumulate excess saliva, drool, develop rhonchi with mild-to-moderate respiratory distress, and demonstrate inability to feed. Workup of EA–TEF is used to confirm diagnosis, plan for surgical intervention, and look for associated anomalies. On workup, infants with EA–TEF will fail to have a 10 F tube pass beyond 10 cm from the lips. On gentle insufflation of the esophageal tube, the size and shape of the

**TABLE 13-1: Gross and Ladd Classification Schemes for Esophageal Atresia and Tracheoesophageal Fistulas**



| Description | EA with distal TEF | Isolated EA | "N-type" TEF | EA with proximal TEF | EA with proximal and distal TEF |
|---|---|---|---|---|---|
| Gross Classification | C | A | E | B | D |
| Ladd Classification | III/IV[a] | I | | II | V |
| Frequency (%) | 86.5 | 7.7 | 4.2 | 0.8 | 0.7 |

EA, esophageal atresia; TEF, tracheoesophageal fistula.

[a]Type III fistula enters above tracheal bifurcation; type IV fistula enters at carina.

*Source:* Reproduced with permission from Goldstein AM, Doody DP, Donahoe PK. Esophageal atresia and tracheoesophageal fistula. In: Pearson FG, Cooper JD, Deslauriers J, et al. *Esophageal Surgery*, New York: Churchill Livingstone, 2002. Copyright Elsevier.

esophageal pouch can be delineated on plain radiographs. Furthermore, dilute barium through the tube or air in the stomach may confirm TEF. The presence of a "gasless" abdomen suggests EA without TEF. Some centers favor endoscopy in an effort to identify a TEF and place a stent prior to surgical repair.

Diagnostic investigations for associated anomalies for patients diagnosed antenatally may include fetal echocardiogram and karyotyping. In the absence of dysmorphism and urinary difficulties, a chest plain film to evaluate vertebral anomalies and echocardiogram may be sufficient. Some centers include a renal ultrasound routinely.

If undiagnosed, infants suffer from aspiration and subsequent respiratory distress and cyanosis during feedings. In severe cases of aspiration, infants may become apneic and bradycardic with subsequent cardiopulmonary arrest. Infants with a distal TEF may develop more severe pulmonary infections and pneumonitis with subsequent severe respiratory distress since gastric secretions reflux into the tracheobronchial tree.

Delayed diagnosis of EA–TEF with survival beyond 25 days of life is rare but has been reported.[17] Because the esophagus remains in continuity, delay in diagnosis is more common for N-type TEF. These infants will present with recurrent cough on feeding, recurrent pneumonias, cyanosis, increased flatulence, and intermittent abdominal distention.

## Preoperative Management

Preoperative management of infants with EA–TEF includes suctioning with an esophageal tube, nil per os, and head of bed elevation to reduce regurgitation and aspiration risk. Intravenous access should be obtained, and maintenance intravenous fluids initiated. In the event of intubation, gastric distention can be reduced by positioning the tip of the endotracheal tube distal to any TEF. Although rare, gastric distention with subsequent perforation is a catastrophic complication, requiring emergency ligation of the distal TEF.

## Surgical Management

Primary repair of EA–TEF is readily achieved through an extrapleural approach via a right posterolateral, muscle-sparing thoracotomy in the fourth intercostal space (Fig. 13-1). The TEF is identified and divided, and the tracheal cuff oversewn. The upper pouch and distal esophagus is identified and mobilized, and then repaired in a primary fashion using interrupted absorbable sutures. Advancement in minimally invasive techniques and technology has made thoracoscopic surgery a viable alternative to standard open repair for EA–TEF. Some series have shown equivalent results to open surgery, although long-term data are elusive.[18,19]

The presence of 13 ribs or a short upper pouch suggests a "long gap." Many strategies have been adopted to tackle the long gap and subsequent anastomotic tension. These approaches have had varying results and include circular or spiral myotomies, mobilization of the distal esophagus, and tubularization of an upper pouch flap.[20–23] Optimal repair for this group of patients is controversial, although a number of centers are now advocating retention of the native esophagus and the benefits of delayed primary repair.[24]

## Postoperative Complications

Anastomotic leak, which occurs in 15 to 20 percent cases, and subsequent sepsis remains a common and serious complication of EA–TEF repair in the early postoperative setting.[25] These infants may present with tension pneumothorax requiring thoracostomy tube placement and/or reoperation to oversew the leak. Smaller leaks are more common, and can be managed conservatively, but may lead to stricture or recurrent fistula in the long term.

Mid-to-long-term postoperative complications include feeding difficulty, fistula recurrence, strictures, reflux, and aspiration. Feeding difficulties are common after repair of EA–TEF and are thought to be secondary to esophageal dysmotility, leading to reflux and potentially aspiration. Some children require enteral nutrition through nasogastric or postpyloric feeding. The incidence of fistula recurrence is likely improved from 5 to 15 percent, historically quoted due to improved techniques, imaging, and instruments. Risk factors predisposing to recurrence include a primary EA–TEF repair under tension and an anastomotic leak.[26] TEF recurrence is suspected when a child develops multiple lower respiratory tract infections with mediastinal air outlining the esophagus on chest radiograph. Surgery is required to correct the recurrent TEF. Up to half of all anastomotic leaks may be complicated by esophageal stricture, and anywhere from 6 to 40 percent of patients develop stricture following EA–TEF repair. An anastomosis under tension, devascularization of the distal esophagus on mobilization, and gastroesophageal reflux are all thought to play a role in the development of esophageal stricture following EA–TEF repair. Most of these patients will require serial esophageal dilations. Up to 40 percent of patients following EA–TEF repair will develop gastroesophageal reflux, half of which are successfully managed with medical therapy, and the remaining may require fundoplication.[27]

# ESOPHAGEAL DUPLICATION CYSTS

## Epidemiology

Esophageal duplication cysts are benign cystic masses that are usually spherical or tubular structures adhering to the esophagus and represent 10 to 15 percent of foregut duplication cysts and 5 to 10 percent of mediastinal cysts. The true incidence of esophageal duplication cysts is unknown.

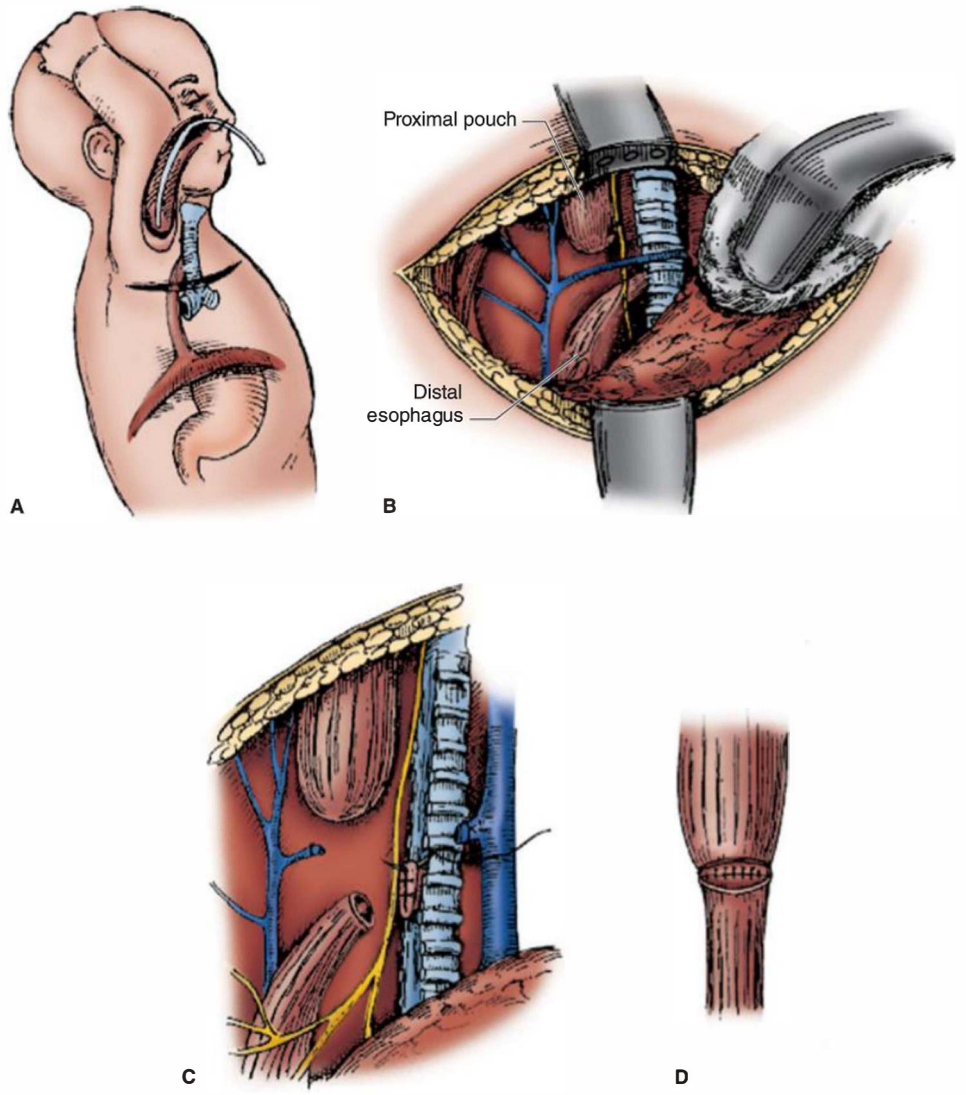



**FIGURE 13-1** Surgical repair of type I esophageal atresia. **A.** A right posterolateral thoracotomy through the fourth intercostal space is a standard approach. **B.** The proximal esophageal pouch and distal esophagus are exposed with anterior traction of the lung and mediastinal pleura. **C.** Division and closure of the tracheoesophageal fistula. **D.** Single-layer primary anastomosis between the proximal and distal esophageal segments using interrupted absorbable sutures. (Reproduced with permission from O'Neill JA. *Operative Surgery, Principles and Techniques,* 3rd ed. Philadelphia: Saunders, 1990:1072. Copyright Elsevier.)

## Embryology

Esophageal duplication cysts arise from errors in foregut budding during the third through sixth week of gestation. During development, the laryngotracheal groove divides into dorsal (esophagus) and ventral (respiratory tract) parts. Esophageal duplication cysts arise when epithelial cell secretory vacuoles, during esophageal development, fail to coalesce.[28] When the budding error occurs determines the location of the cyst.

## Classification, Clinical Presentation, and Diagnosis

Esophageal duplication cysts are cystic remnants of the foregut lined with gastrointestinal epithelium and covered by two layers of smooth muscle. Histologically, the gastrointestinal epithelial lining of esophageal duplication cysts can be composed of squamous, columnar, cuboidal, pseudostratified, or ciliated cells. They can occur in the cervical, thoracic, or abdominal segments. Luminal communication is uncommon.

Many patients with esophageal duplication cysts are asymptomatic and never diagnosed. Approximately, 25 percent are children. When symptoms develop, they result from tracheal and esophageal compression and include chest fullness, dysphagia, and/or hematemesis. When the cyst involves the upper esophagus, obstructive symptoms are more prevalent. Anorexia, weight loss, regurgitation, gastrointestinal bleeding, vomiting, cough, recurrent pneumonitis, and chest pain may also occur. In certain cases, patients with esophageal duplication cysts are at risk for bleeding, ulceration, and cyst rupture. If the esophageal cyst ruptures, patients may develop mediastinitis. Associated anomalies include neural or gastrointestinal anomalies. Adults are usually asymptomatic, but if left untreated, usually develop symptoms.

It is important to differentiate esophageal duplication cysts from other mediastinal masses, including bronchogenic cysts and malignancies. Most esophageal duplication cysts are found in the right posterior–inferior mediastinum and are often detected incidentally on plain chest radiographs as a large, unilateral, sharply defined, spherical, or tubular mass. The mass may displace the trachea and/or esophagus. To confirm the diagnosis, barium contrast esophagography can be performed demonstrating a filling defect with distortion of the lumen. Unfortunately, esophagography is poor at distinguishing cystic from solid tumors. On CT, esophageal duplication cysts are located in the posterior mediastinum, are round, homogenous, have smooth margins, do not invade adjacent structures, and do not enhance with contrast. Once CT has been performed, esophagoscopy should be performed to rule out abnormal appearing mucosa overlying the cyst. Endoscopic ultrasound can also be used to define the cyst as intra- or extramural, and to help delineate cystic versus solid tumor. These cysts should not be aspirated given the risk of infection. Cysts with gastric epithelial lining that present with ulceration or bleeding can be revealed with technetium scanning.

### Surgical Management

All patients with symptomatic esophageal duplication cysts require resection and pathologic workup to rule out malignancy. In a high-risk patient with a definitive diagnosis of esophageal duplication cyst, conservative management is a reasonable option. On the other hand, in the good surgical candidate, surgical resection is advised to avoid cyst enlargement and subsequent compression, ulceration, bleeding, infection, rupture, or malignancy.

The approach to surgical resection may involve a limited posterolateral thoracotomy or video-assisted thoracoscopy. A minimally invasive approach may be more appropriate, given the lesions are benign and often easily dissected. Intramural cysts are enucleated by dividing overlying esophageal musculature while maintaining esophageal wall integrity. In the event the cyst is in continuity with the esophageal lumen, the continuity should be closed and the esophageal wall reapproximated carefully to avoid stricture.

## ESOPHAGEAL STENOSIS AND WEBS

### Epidemiology

Congenital esophageal stenosis occurs in 1 in 25,000 to 50,000 live births.[29]

### Embryology

The embryologic origin of esophageal stenosis and webs is unknown. The most common etiology is fibromuscular thickening. Other common causes include tracheobronchial remnants due to incomplete separation of the primitive foregut and respiratory tract, as well as congenital webs from failure of complete vacuolization of the primitive esophageal lumen.

### Classification, Clinical Presentation, and Diagnosis

Congenital esophageal stenosis can be classified on an anatomic basis into fibromuscular thickening, tracheobronchial remnants, and membranous web. Those that result from fibromuscular thickening have diffuse fibrosis of the esophageal wall with hypertrophy of the muscularis and submucosal layers. These stenoses are located commonly in the distal esophagus, and therefore are commonly associated with EA. Stenoses due to tracheobronchial remnants are also located in the distal esophagus and contain cartilage, respiratory mucous glands, or ciliated epithelium. These remnants form a rigid and focal stenosis. Membranous webs, the rarest of congenital esophageal stenoses, consist of a thin membrane lined with epithelium and have an eccentrically located opening. Membranous webs are found in all segments of the esophagus.

Congenital esophageal stenosis will present in infants as progressive dysphagia and postprandial emesis. Severity of disease depends on the location and degree of stenosis: A proximal stenosis leads to an inability to swallow solid food, a distal stenosis results in regurgitation, and a complete stenosis/obstruction resembles infants who present with EA. Diagnosis is based on barium esophagography and endoscopy, which can define the location and severity of stenosis.

### Management

Treatment of congenital esophageal stenosis revolves around treating symptoms. Initially, esophageal dilatation using Maloney or Avaray bougies can be used to treat children with thin esophageal webs or mild fibromuscular thickening. Dilatation is not without complications, which include esophageal leak and recurrent stenosis

requiring repetitive dilatations to maintain patency. If conservative management fails, resection with primary end-to-end anastomosis is performed. The approach is usually through a right thoracotomy for middle-third stenoses, or a left thoracotomy for distal stenoses. If the stenosis is near the gastroesophageal junction, a concomitant antireflux procedure should be performed.

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## CONGENITAL ESOPHAGEAL ANOMALIES BOARD REVIEW QUESTIONS (CHAPTER 13)

1. Which of the following is correct regarding esophageal atresia?
   A. The incidence is 1 in 200.
   B. There is a slight preponderance in females.
   C. Chromosomal abnormalities have been reported in nearly 50 percent of cases.
   D. About 10 percent will be associated with other anomalies.
   E. The CHARGE association includes cardiac defects.

2. Which anatomic configuration is most common?
   A. Esophageal atresia with distal tracheoesophageal fistula
   B. N-type tracheoesophageal fistula
   C. Esophageal atresia with proximal tracheoesophageal fistula
   D. Esophageal atresia with both proximal and distal tracheoesophageal fistula
   E. Isolated esophageal atresia

3. Which is true regarding complications after surgery for esophageal atresia?
   A. Anastomotic leak occurs in 5 to 10 percent.
   B. Feeding difficulties are uncommon.
   C. The incidence of fistula recurrence has not improved overtime.
   D. Up to 25 percent of all anastomotic leaks are complicated by stricture.
   E. Gastroesophageal reflux occurs in nearly 40 percent of patients.

4. Which is correct regarding esophageal duplication cysts?
   A. These cysts are considered premalignant.
   B. They represent 5 to 10 percent of all mediastinal cysts.
   C. They result from abnormal foregut budding during the sixth and ninth weeks of gestation.
   D. The cyst is lined with gastrointestinal epithelium and does not have a smooth muscle covering.
   E. Luminal communication is common.

5. Which is correct regarding diagnosis of esophageal duplication cysts?
   A. Most patients are asymptomatic.
   B. Over 75 percent present in children.
   C. Obstructive symptoms are more common when the cyst involves the lower esophagus.
   D. Most are located in the left posterior–inferior mediastinum.
   E. These cysts should be aspirated for cell analysis.

## ANSWERS

1. **Answer: D.** The CHARGE associated defects include coloboma, heart, atresia choanae, retarded development, genital hypoplasia, and ear abnormalities. The incidence of esophageal atresia is about 1 in 3400 and there is a slight preponderance in males. Chromosomal abnormalities occur in 6 to 10 percent cases and up to 60 percent will have other associated anomalies.
2. **Answer: A.** Esophageal atresia with distal tracheoesophageal fistula is the most common configuration, occurring in over 85 percent cases.
3. **Answer: E.** Gastroesophageal reflux is common, occurring in up to 40 percent of patients after operative repair. Anastomotic leak occurs in 15 to 20 percent, and half of these will be complicated by stricture. Feeding difficulties are common after surgical repair. The incidence of fistula recurrence likely has improved with modern techniques and instrumentation.
4. **Answer: B.** Esophageal duplication cysts represent 5 to 10 percent of all mediastinal cysts. These are benign cysts that result from abnormal foregut budding during the third and sixth weeks of gestation. The cyst is lined with gastrointestinal epithelium and is covered with two layers of smooth muscles. Luminal communication is uncommon.
5. **Answer: A.** Most patients are asymptomatic and are diagnosed incidentally. Only 25 percent present in children. Obstructive symptoms are more common when the cyst involves the upper esophagus. Most are located in the right posterior–inferior mediastinum. These cysts should not be aspirated to avoid infection.

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14

# Gastroesophageal Reflux Disease and Esophageal Motility Disorders

*Shelly Bansal*
*Brian Goodman*
*Edmund S. Kassis*

## KEY CONCEPTS

- Epidemiology
  - Gastroesophageal reflux disease (GERD) is one of the most frequently encountered problems seen in clinical practice today. It is estimated that 60 million adults report suffering from reflux symptoms at least once a month. Almost 24 percent of the population report heartburn daily and 43 percent have weekly episodes.
  - Achalasia is a disease affecting 1/10,000 people, making it the second most common esophageal motility disorder. It affects men and women equally from the ages of 20 to 40 years.
- Pathophysiology
  - GERD develops when the normal protective barrier of the esophagus is overcome and exposed to chronic insult. The pathogenesis of GERD is multifactorial, including anatomic factors, motor abnormalities, impaired esophageal clearance, and altered mucosal resistance.
  - Achalasia is a result of neuronal degeneration of the myenteric plexus. The consequence is an unopposed sympathetic response and increased pressure at the level of the lower esophageal sphincter (LES), leading to a functional obstruction of the esophagus.
- Clinical features
  - GERD is variable in its presentation. Heartburn, regurgitation, and chest pain are the most common complaints. Extraesophageal symptoms include pneumonia, airway inflammation, chronic cough, laryngitis, and hoarseness.
  - Achalasia presents as progressive dysphagia, initially presenting with dysphagia to solids and then to liquids.
- Diagnostics
  - Diagnostic studies for GERD include 24-hour pH monitoring, BRAVO probe, endoscopy, and manometry.
  - The pathognomonic finding in achalasia is of a "bird's beak" on esophagogram. Manometry is the gold standard for achalasia. Classic findings are a hypertensive LES (resting pressure >45 mm Hg), incomplete relaxation of the LES with swallowing, residual pressure >8 mm Hg, and esophageal aperistalsis.
- Treatment
  - Initial management of GERD includes lifestyle medication and proton pump inhibitors (PPIs). Failure of medical therapy or inability to tolerate PPIs is an indication for surgery. Laparoscopic Nissen fundoplication is the surgery of choice. Alternate options include partial fundoplication or Collis gastroplasty for patients with esophageal motility disorders or a short esophagus.
  - Multiple options for the treatment of achalasia include smooth muscle relaxants, dilation, botulinum toxin, and Heller myotomy.
- Outcomes
  - Laparoscopic Nissen fundoplication has shown equal efficacy to an open approach in controlling GERD and is associated with decreased length of stay (LOS), less pain, and lower costs. The overall complication rate is between 5 and 10 percent. Laparoscopic antireflux surgery (LARS) is associated with an improvement in symptoms compared with those treated medically but is associated with a 6-percent rate of severe dysphagia.
  - Laparoscopic Heller myotomy has been shown to be superior to botulinum toxin injection and pneumatic dilation. Recent series show excellent long-term relief of symptoms at 2 years.

## INTRODUCTION

Gastroesophageal (GE) reflux is a normal physiologic process whereby gastric and pancreaticobiliary secretions reflux into the esophagus. This process becomes pathologic when the normal response to reflux fails and symptoms ensue. Gastroesophageal reflux disease (GERD) is one of the most frequently encountered problems seen in clinical practice today. The American College of Gastroenterology estimates that roughly 60 million adults report suffering from reflux symptoms at least once a month.[1] Almost 24 percent of the population report heartburn daily and 43 percent have weekly episodes.[2] The reported incidence of GERD has nearly doubled in the last 3 decades,[3] with current annual expenditure on proton pump inhibitors (PPIs) in excess of US$ 14 billion.[4]

## PATHOPHYSIOLOGY

### Lower Esophageal Sphincter

GERD develops when the normal protective barriers employed by the esophagus are overcome, exposing it to repeated and chronic insult. A crucial role in the pathogenesis of GERD is mediated by contact of the esophageal mucosa with refluxate that can be composed of acid, bile, and pancreaticobiliary secretions. The mechanisms involved in the pathogenesis of GERD are multiple and include anatomic factors, motor abnormalities, impaired esophageal clearance, and altered mucosal resistance.

### Anatomic Barrier

The lower esophageal sphincter (LES) is a 3- to 4-cm segment of distal esophagus.[5] This high-pressure zone remains under tonic contraction, with resting pressures maintained at 10 to 30 mm Hg. Although large fluctuations are seen during a 24-hour period, resting pressure does not directly correlate with the severity of reflux.[6]

The LES mechanism has three distinct characteristics: sphincter length, pressure, and location.[7] The overall intra-abdominal length of the LES is of crucial importance to the esophageal surgeon. A decrease in overall length or intra-abdominal LES correlates directly with the degree of LES incompetence (Fig. 14-1).[8] In addition, the location of the LES is also important in maintaining competence. The LES is subject to elevated pressures, but due to its intra-abdominal position, the sphincter collapses and prevents reflux.[6]

### Acid Clearance and Bile Exposure

Normal acid clearance is dependent on esophageal motility. Esophageal dysmotility is found in 40 to 50 percent of the GERD population.[9] In these patients, decreased clearance leads to increased acid and bile exposure, resulting in esophagitis, stricture, and initiation of malignant degeneration.[9]

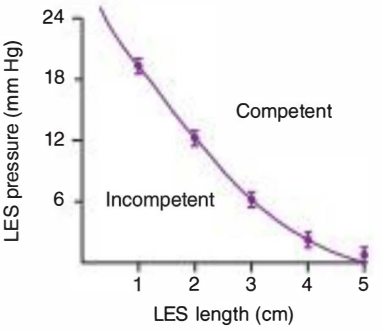



**FIGURE 14-1** The relationship between the pressure and length of the LES. Note that the shorter the overall length of the high-pressure zone, the higher the pressure must be to maintain sufficient resistance to be competent. (From DeMeester TR. Evolving concepts of reflux: The ups and downs of the LES. *Can J Gastroenterol* 2002;16(5):327–331. With permission.)

### Hiatal Hernias

Hiatal hernias are frequently found in patients with GERD and are present in 70 to 90 percent of patients with severe reflux. In the presence of a sliding hiatal hernia, the compression of the crus and the angle of His are disrupted. Hiatal hernias change the acute angle produced by the angle of His and disrupt the flap valve mechanism that prevents reflux.[6] In addition, a hiatal hernia results in dilation of the diaphragmatic crus and loss of the extrinsic compression provided by the diaphragm on the GE junction.[10] Migration of the stomach into the chest results in the disassociation of the LES from the crural diaphragm, resulting in failure of the antireflux barrier. The disruption of the GE junction lowers the threshold for LES relaxation, worsens positional reflux, diminishes esophageal clearance, and acts as a reservoir for gastric and duodenal secretions.[11]

### Causes of GERD and Progression

In a normal individual, lower esophageal relaxation occurs after a swallow. The swallow decreases LES tone to allow entry of food or fluids into the stomach. In GERD, transient LES relaxation or TLESRs are found to be the underlying cause of pathologic reflux.[12] TLESRs are defined as brief episodes of LES relaxation that are unrelated to swallowing or peristalsis. Neurophysiology studies indicate that TLESRs are visceral reflexes with vagal afferent and efferent pathways that transmit information to and from the dorsal nucleus of the vagus.[10] Gastric distension, by stimulation of proximal gastric tension and stretch receptors, has been recognized as a major factor inducing TLESRs.[5] TLESRs are found in both normal individuals without symptomatic reflux and those with GERD.

With increasing frequency of these episodes, mucosal inflammation follows. Inflammation and injury lead to shortening of the esophagus. This critical point is termed as the permanently defective LES.[7] Characteristics include an

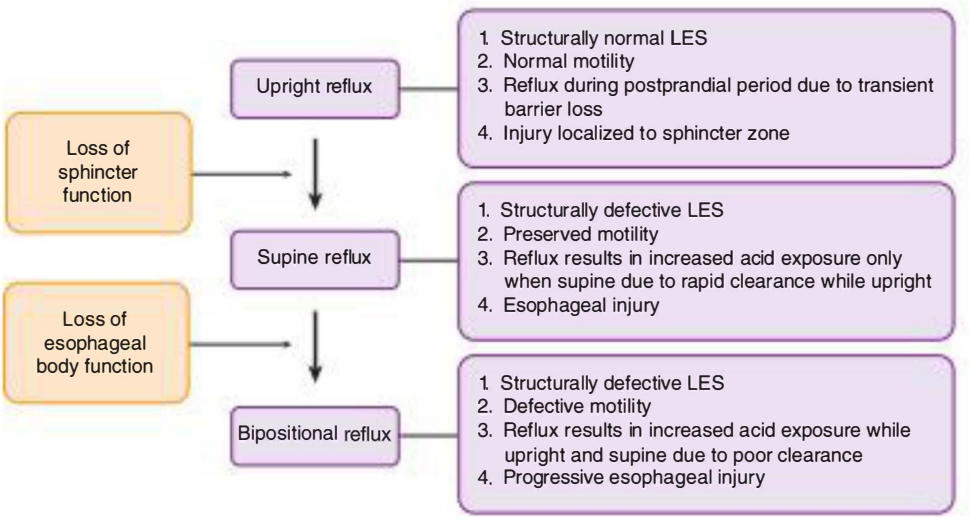



**FIGURE 14-2** Schema for progression of GERD. Initially, esophageal acid exposure occurs only in the upright awake position after meals due to gastric distension causing TLESRs. With inflammatory changes of the LES, the barrier becomes permanently defective, and an increase in esophageal acid exposure occurs in the supine position, while the esophageal body effectively clears the refluxed acid during the day. Inflammatory injury to the esophageal body results in loss of the esophageal body clearance function or bipositional reflux. (From DeMeester TR. Evolving concepts of reflux: The ups and downs of the LES. *Can J Gastroenterol* 2002;16(5):327–331. With permission.)

average pressure less than 6 mm Hg, length less than 2 cm, and an intra-abdominal length less than 1 cm.[7] As the cycle continues, advanced GERD becomes a more difficult disease process to manage medically; while symptoms may be controlled by acid suppression, reflux is still present (Fig. 14-2). This continued exposure can lead to the Barrett's metaplasia, stricture, and cancer.

## SYMPTOMS

The presentation of GERD is highly variable and symptoms are divided into two broad categories: esophageal and extraesophageal symptoms. Heartburn and regurgitation are the most common complaints. The classic presentation is retrosternal pain occurring 30 to 60 minutes after a meal, particularly in the recumbent position. The combination of both heartburn and regurgitation is 90 percent accurate in the diagnosis of GERD. Odynophagia and dysphagia are other common esophageal symptoms. Alarm symptoms include unintended weight loss, hematemesis, black or bloody stool, and recurrent vomiting. They are present in about 10 percent of patients presenting to primary care and require urgent endoscopy.[13]

Extraesophageal symptoms are increasingly being linked to reflux disease.[14] In most cases, the symptoms are not recognized. Pulmonary complications due to aspiration of gastric contents into the pulmonary system lead to pneumonia, airway inflammation, and chronic cough. Reflux that reaches the oral cavity can result in water brash, sour taste in the mouth, and dental erosions. Finally, reflux to the vocal cords can result in laryngitis and hoarseness.[14]

## DIAGNOSIS

A patient with typical symptoms, such as heartburn and regurgitation, can be diagnosed with GERD, and a trial of acid-reducing medications is indicated.[15] Although not a truly diagnostic technique, response to empiric therapy with PPIs is strongly suggestive of GERD and is also a predictor of patients who benefit from antireflux surgery. A recent American Gastroenterological Association position statement supports the use of diagnostic testing for esophageal reflux to (1) avoid misdiagnosis, (2) identify complications of reflux disease, and (3) evaluate empirical treatment failures.[11] Patients with atypical symptoms or who have failed medical therapy require additional testing.

Flexible endoscopy is essential in the evaluation of GERD. Endoscopic findings of a "mucosal break" or areas of slough or erythema demarcated from adjacent normal-appearing mucosa are confirmatory findings of esophagitis. Furthermore, it is mandatory to obtain mucosal biopsies to exclude malignancy. Endoscopy can also be used to grade the degree of disruption of the flap valve mechanism.[16] This is done on a retroflexed view of the GE junction. The flap valve is graded according to the Hill classification (Hill grade 1–4; 1 = normal closed valve, 4 = open valve, associated hiatus hernia).[16]

Twenty-four-hour pH monitoring is the gold standard test to evaluate reflux esophagitis. A pH probe is placed 5 cm above the manometrically determined LES. The probe records the total number of acid exposures with a pH less than 4, total acid-exposure time, upright and supine episodes, number of reflux episodes, number of episodes lasting greater than 5 minutes, and the duration of the longest episode. An overall composite score is calculated and can be

used to quantify the severity of GERD. Simpler methods to determine abnormal reflux can be used and can be calculated by finding the percent time the pH is less than 4; in normal individuals, this should be less than 4 percent.[17]

Finally, manometric testing is required particularly in patients who are being considered for surgical intervention. Esophageal manometry is performed by inserting a water-perfused catheter into the esophagus and then withdrawing the catheter as the patient swallows. Manometry gives information regarding the location, pressure, and length of the LES. Manometry also helps to assess the esophageal body and the effectiveness of peristalsis. Normally, a patient should have 80 percent successful swallows but when that number drops to 60 percent, the diagnosis of ineffective esophageal dysmotility is given.[18]

Newer techniques for esophageal functional testing such as wireless pH capsule monitoring, duodenogastroesophageal reflux (formerly referred to as alkaline or bile reflux) detection, and esophageal impedance testing have been introduced over the past decade. These techniques have been shown to have superior sensitivity and recording accuracy and provide more information to predict patients most at risk for future complications.[19]

## MEDICAL MANAGEMENT

Medical management of GERD is severity based. Most patients with mild symptoms can be treated with lifestyle modification including smoking cessation or weight loss, while others may be treated with over-the-counter antacids or $H_2$-blockers for the prevention of occasional symptoms of reflux.[15] Patients with moderate-to-severe symptoms require scheduled pharmacotherapy. Antisecretory drugs are strongly recommended for both symptomatic relief and healing of erosive esophagitis. PPIs have been shown to be superior to $H_2$-receptor antagonists and are normally 90 percent effective in treating erosive esophagitis. There is good evidence that twice-daily PPI therapy may be an effective treatment in patients who fail daily therapy. Most patients are treated for 8 to 10 weeks, and although they will heal, many will relapse in 6 to 9 months if taken off therapy (Fig. 14-3). Debate still

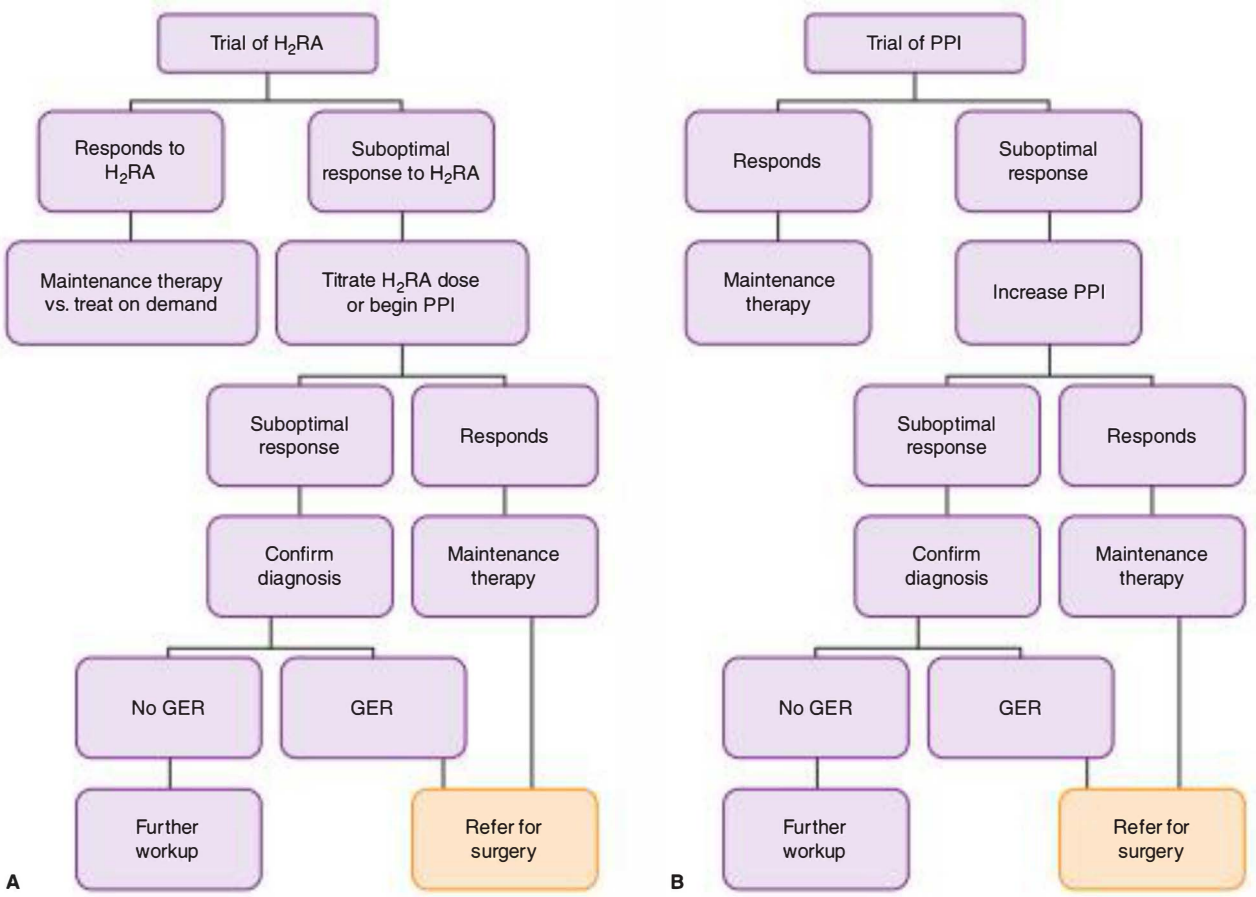



**FIGURE 14-3** Management algorithm for treatment of uncomplicated (**A**) and complicated (**B**) gastroesophageal reflux (based on endoscopic findings). $H_2$RA, $H_2$ receptor antagonist. (From Smith CD. *Surg Gastrointest Endosc Clin N Am* 2009;19(1):35–48. With permission.)

surrounds the optimal management of the patient who suffers from GERD, but it is now well accepted that surgical intervention is an alternative and possibly a superior option for many patients with reflux disease.[20]

## SURGICAL INDICATIONS

An indication for antireflux surgery is often a failure to respond to or inability to tolerate PPI therapy. The best evidence for efficacy of surgery exists for patients with severe esophagitis and/or excessive distal esophageal acid exposure when PPI therapy is held.[11] Patients who are symptomatic after 3 months of medical therapy with stricture, aspiration, or bleeding, or those who have a large hiatal hernia are candidates for an antireflux procedure. It is important to document the correct diagnosis and demonstrate the presence or absence of esophageal dysmotility. All surgical candidates should undergo manometry and pH testing.

## PRINCIPLES OF SURGERY

The goals of antireflux surgery are to reestablish the LES pressure, relocate the LES within the abdomen, and finally close any hiatal defect. The laparoscopic Nissen fundoplication has emerged as the procedure of choice in antireflux surgery. When done either open or laparoscopically, the key elements of the Nissen fundoplication include the following:

1. Complete dissection of the esophageal hiatus and both crura
2. Mobilization of the gastric fundus by division of the short gastric vessels
3. Closure of the hiatal defect by nonabsorbable sutures
4. Creation of a tensionless 360-degree gastric wrap at the distal esophagus around a 50-to-60-F bougie
5. Creation of a 1.5- to 2-cm wrap with the distal suture incorporating the anterior position of the stomach.[21]

With multiple modern trials that have now been published, there are data that show laparoscopic antireflux surgery (LARS) is more cost-effective and results in better overall symptom control than medical management.[20,22,23] Long-term data continue to accrue and suggest that laparoscopic Nissen fundoplication has become the standard for surgical treatment of GERD, with improved morbidity, length of stay, and return to work.[24] Every attempt should be made preoperatively to determine the degree of abdominal esophageal length to allow for a tension-free fundoplication. If sufficient intra-abdominal length is not available, an esophageal-lengthening procedure should be performed. Concern about esophageal motility could also influence operative strategy. Studies have shown that preoperative evidence of motility problems may or may not be associated with higher rates of dysphagia.[21] This has prompted some surgeons to choose a 270-degree fundoplication (Toupet) that other studies have validated as having a decreased incidence of reoperation for failure (usually due to dysphagia).[24]

## TECHNIQUE

### Laparoscopic Nissen Fundoplication

After intubation and decompression of the stomach with a nasal or orogastric tube, the patient is laid in a supine position. Pneumoperitoneum of 15 mm Hg is established and five trocars are placed. Exposure of the hiatus starts with deploying a fan retractor to retract the left lobe of the liver. The gastrohepatic ligament is incised, and the right crus of the diaphragm is identified. The esophagus is dissected away from the right crus of the diaphragm. The phrenoesophageal ligament is incised with care to protect the anterior vagus nerve. The dissection is carried to the left crus. We then carry the dissection into the mediastinum. Once complete, the crural and mediastinal dissection should allow for 2 to 3 cm of tension-free intra-abdominal esophagus. If the length of intra-abdominal esophagus is inadequate, an esophageal-lengthening procedure should be performed.[21] Attention is then turned to the division of the short gastric vessels and mobilization of the fundus of the stomach. The lesser sac is entered and the short gastrics are divided by a harmonic scalpel. A window is then created posterior to the esophagus while avoiding injury to the posterior vagus nerve. The fat pad is dissected off the GE junction. A 50- to 56-F bougie is then passed to allow for appropriate sizing of the fundoplication. A grasper is then passed through the posterior window, and the fundus is pulled through the window. Care should be taken to ensure that the mobilized fundus is under no tension. Both edges of the wrap can be grasped and gently "shoeshined" back and forth to check adequate length and tension. The fundus is then approximated anterior to the esophagus using full-thickness bites of nonabsorbable suture. The fundoplication length should be 1.5 to 2 cm.[25] Each stitch should incorporate partial thickness of the distal esophagus. The bougie is then removed and the crural defect is closed with heavy nonabsorbable sutures (Fig. 14-4).

### Laparoscopic Partial Fundoplication

This is generally performed for patients with concomitant GERD and esophageal motility disorders. The approach to the partial 270-degree fundoplication is essentially the same as the laparoscopic Nissen except for the extent of the posterior wrap. The wrap is secured to the left and right crura.

Transient dysphagia, due to edema, is the most common complication; it occurs in almost half of the population and resolves within 3 weeks of the operation. Wrap failure is another early complication and is attributed to a malpositioned wrap at the time of initial operation. In addition, postoperative retching and nausea has been implicated in wrap migration and should be aggressively managed during the postoperative period.[21] Additional early complications include pneumothorax and esophageal perforation. Reported rates of perforation range from 0 to 4 percent in most series.

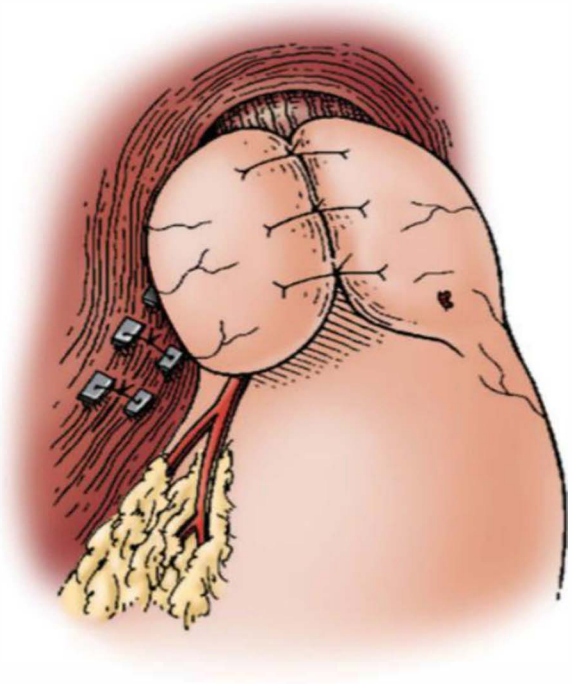


**FIGURE 14-4** Completed Nissen fundoplication. (From Smith CD. *Surg Gastrointest Endosc Clin N Am* 2009;19(1):35–48. With permission.)

## OUTCOMES

Laparoscopic Nissen fundoplication has largely supplanted open fundoplication for surgical management of GERD. The laparoscopic approach has shown equal efficacy with the open approach with respect to long-term management of GERD and is associated with shorter hospitalization, less postoperative pain, faster recovery and return to work, and lower total costs. The overall complication rate is between 5 and 10 percent and includes ileus, pneumothorax, dysphagia, gas bloat, and splenic injury. Multiple studies have reported superiority of LARS over medical management with regard to control of GERD symptoms.[20,22,23] Lundell and colleagues reported a significant rate of sustained remission in surgically treated patients compared with those treated medically. There were significantly more reflux symptoms with medical treatment; however, dysphagia was much more common after surgery.[20] Multiple studies consistently report about a 6-percent rate of severe dysphagia, and other complications include early satiety, abdominal bloating, inability to vomit, and diarrhea. Rates of reoperation reported in US studies were 2.3 to 7 percent.[26] Ultimately, between 10 and 11 percent of patients with either therapy will have recurrent esophagitis,[20] and 30 to 60 percent of patients who have undergone ARS will continue to use antisecretory medication.[27] Most importantly, all available trials to date show relative equivalence between the two therapies with regard to development of Barrett's esophagus or esophageal adenocarcinoma.[26]

## ENDOSCOPIC APPROACHES

Endoscopic treatment currently seems best suited for patients with GERD who are PPI dependent with small (<3 cm) or absent hiatal hernias and have no evidence of severe esophagitis or Barrett's esophagus. Several endoscopic antireflux procedures have been evaluated for the treatment of GERD. Injection of material to augment the LES as well as application of radiofrequency energy has been attempted but failed in the long term and is no longer available. The most promising techniques currently focus on endoluminal suturing/plication.

EndoCinch is a transoral gastroplication system performed under direct visualization. The EndoCinch is inserted through a 9-mm endoscope and a fold of tissue at the GEJ is grasped. A suture is placed through the device, and the device is then rotated, grasping more tissue and plicating the mucosa. The circumference is completed, and four separate plications are completed below the level of the GE junction. The EndoCinch (BARD, Billerica, MA) initially demonstrated efficacy but had problems with suture loss over time, and despite using more sutures, it seems as if the durability of the repair has not been greater than 12 months.[28]

The Plicator (NDO Surgical, Mansfield, MA) was designed to create a transmural full-thickness plication at the angle of His. The plication is formed with a pretied, suture-based implant. This plicating device remodels the antireflux barrier at the angle of His by fashioning a pleat of full-thickness tissue and permitting serosa-to-serosa contact. Data suggest that placement of two to three implants are needed to optimally restructure the GE junction. NDO was subsequently acquired by another company, and the Plicator is no longer available for commercial use.[28]

EsophyX (EndoGastric Solutions, Redmond, Washington) is a large overtube device with an insertion channel for a videogastroscope. The system is designed to create a 270-degree circumferential endoscopic plication at the angle of His by attaching the fundus to the anterior and left lateral wall of the distal esophagus slightly below the esophagogastric junction.[29] The method involves the placement of approximately 6 to 14 sutures to create a near circumferential gastroplication of 180 to 270 degrees.[28] The technique is known as transoral incisionless fundoplication (TIF), and it is being used more often in the United States. There are published studies with 24 months of follow-up in Europe with assessment of all outcomes in each patient showing that 79 percent of patients experienced complete cure (29 percent) or remission (50 percent) of GERD at 2 years.[29]

## ACHALASIA

Achalasia is a result of neuronal degeneration of the myenteric plexus. The consequence is an unopposed sympathetic response and increased pressure at the level of the LES, leading

to a functional obstruction of the esophagus.[30] If left untreated, the esophagus progressively dilates and becomes aperistaltic.

## Pathology

The etiology of primary achalasia is unknown, but pathologic findings show diminished myenteric ganglion, collagen deposition, and lymphocytic infiltration. Given these findings, some consider a virus to be the cause of achalasia.[30] Another theory implicates decreased levels of nitric oxide synthase, suggesting that achalasia is an autoimmune disorder rather than a viral one.[31] A common cause of secondary achalasia is Chagas disease, passed by the protozoan *Trypanosoma cruzi*. It infects the intramural neurons, resulting in autonomic dysfunction and elevated LES pressures. Finally, psuedoachalasia is another entity in which the LES is infiltrated by cancer, resulting in inadequate LES relaxation.

Achalasia is a premalignant condition. Longstanding mucosal irritation due to stagnant undigested food leads to metaplasia and finally frank carcinoma. Squamous carcinoma occurs in 2 to 8 percent of patients with longstanding achalasia.[32]

## Clinical Features

Achalasia is a disease affecting 1/10,000 people,[32] making it the second most common esophageal motility disorder. It affects men and women equally from the ages of 20 to 40 years.[33] It is a slowly progressive disease that results in a delay in presentation. The time from onset of symptoms to presentation is approximately 6 years.[34]

The most common symptom is dysphagia; initially, patients have problems with solids foods and then with liquids. In addition, 70 to 80 percent of patients complain of regurgitation of food, which can result in aspiration and chronic pulmonary symptoms. Other common symptoms include chest pain and heartburn. Heartburn can complicate the picture of achalasia and may be present in up to 48 percent of patients.[30] Invariably, these patients are misdiagnosed and treated with PPIs that are usually unsuccessful.[31]

## Diagnosis

A barium esophagogram is often the first study performed for patients with dysphagia. It is diagnostic, showing a dilated esophagus with an air-fluid level and the pathognomonic finding of a "bird's beak" with advanced achalasia (Fig. 14-5A–C). At endoscopy, a dilated esophagus with a tight LES that "pops" open with gentle pressure is seen. Other endoscopic findings include retained food and saliva, but most importantly, endoscopy rules out strictures and obstruction unrelated to achalasia. However, normal endoscopy may be present in 40 percent of patients.[31]

Esophageal manometry is the gold standard diagnostic modality. Classic manometric abnormalities can be identified including hypertensive LES (resting pressure >45 mm Hg),

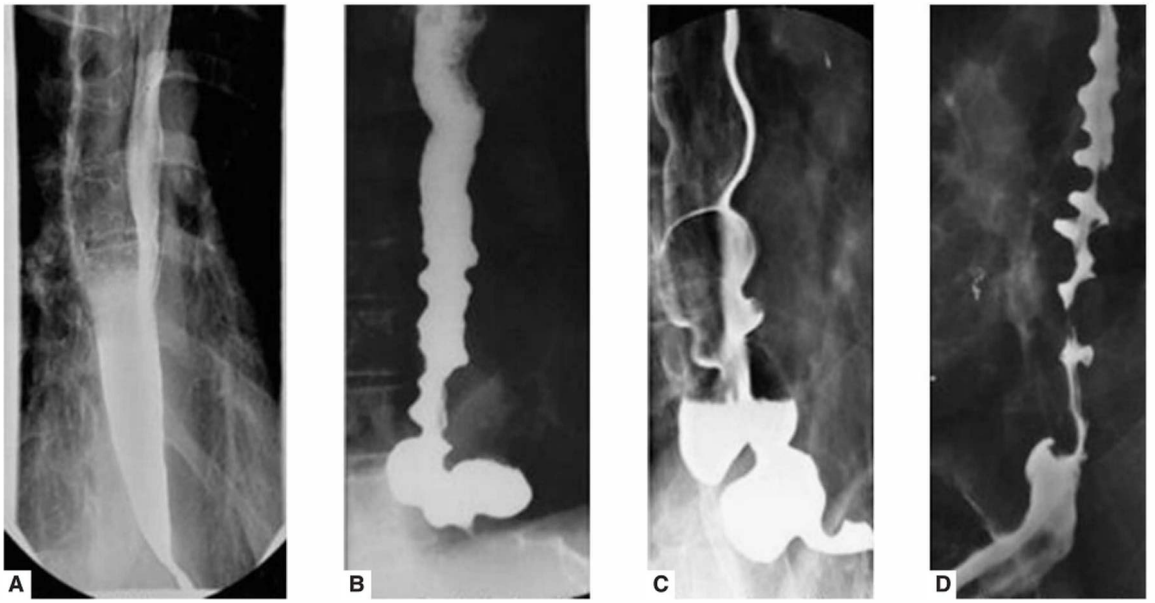



**FIGURE 14-5** Barium esophagograms of achalasia patients demonstrating the classic "bird's beak" (**A**), diffuse narrowing of the esophagus with a spastic appearance often seen in "vigorous" achalasia (**B**), a dilated and tortuous esophagus with early "sigmoidization" of the esophagus observed in long-standing achalasia accompanied by multiple pulsion diverticula (**C**), and the typical "corkscrew" appearance of the esophagus in a patient with diffuse esophageal spasm (**D**). (**A–C**: From Francis DL. Achalasia: Update on the disease and its treatment. *Am Gastroenterol Assoc* 2010;139(2):369. With permission from Elsevier. **D**: From Woltman T. Surgical management of esophageal motility disorders *J Surg Res* 2004;117(1):34–43. With permission.)

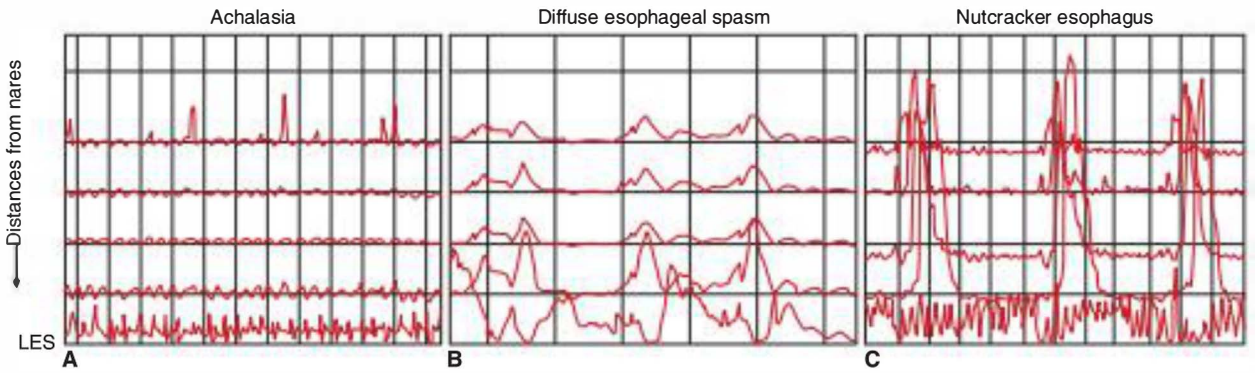



**FIGURE 14-6** Manometry tracing from a patient with achalasia. Notice the lack of peristalsis in the esophageal body and the failure of relaxation of the lower esophageal sphincter (LES) (**A**). A patient with diffuse esophageal spasm (DES), demonstrating simultaneous contractions throughout the esophagus (**B**). Tracing from a patient with nutcracker esophagus (NE) demonstrating high-altitude contractions. Contraction amplitudes measured in mm Hg at different distances from nares (cm) (**C**). (From Woltman T. Surgical management of esophageal motility disorders *J Surg Res* 2004;117(1):34–43. With permission.)

incomplete relaxation of the LES with swallowing, residual pressure > 8 mm Hg, and esophageal aperistalsis (Fig. 14-6A).[30] A variant of achalasia, vigorous achalasia, has similar findings of an aperistaltic esophagus, but with associated high-amplitude contractions (60 mm Hg). High-resolution manometry is an alternate and newer diagnostic modality that will aid in the diagnosis of achalasia (see Chapter 12). Still in its infancy, it may yield superior and reproducible results in the future.[35]

## Medical Therapy

Since the cause of achalasia is unknown, treatment is directed toward symptom relief. Medical treatment options include oral nitrates and calcium channel blockers in an attempt to facilitate LES relaxation. Therapy is usually ineffective since most patients are unable to tolerate the side effects that include headaches, hypotension, and tachyphylaxis. Therefore, medical therapy is generally reserved for patients who are not candidates for surgical intervention.[32]

Endoscopic botulinum toxin and pneumatic dilatation are alternate options. Endoscopically injected botulinum toxin blocks the release of acetylcholine, resulting in lower resting and basal LES pressures.[33] Although botulinum toxin is effective in approximately half of the patients at 6 months, the rest require multiple injections.[34,36] Repeated injections of botulinum toxin results in an inflammatory response at the LES, making later surgical intervention difficult. Most surgeons agree that botulinum toxin should be reserved for patients who are not surgical candidates.[31,33] Pneumatic dilation is another option. Dilation is aimed at fracturing the muscularis propria.[31] Pneumatic dilation carries a 2-to-7-percent risk of complication and a mortality rate of less than 1 percent.[37]

A recent Cochrane review compared pneumatic dilation with botulinum toxin and found pneumatic dilation to be a much better option. Symptom reoccurrence was reviewed at 1, 6, and 12 months. Seventy percent of patients who underwent botulinum toxin had symptom recurrence and treatment failure at 12 months versus 30 percent who underwent dilation.[38] Therefore, current data only support the use of botulinum in patients who are unfit for surgery or as a bridge to definitive therapy.

## Surgical Myotomy

Surgical myotomy is the procedure of choice in patients diagnosed with achalasia who do not have multiple medical comorbidities. The Heller myotomy was first introduced in 1913 by Ernest Heller. The original Heller myotomy was performed using both an anterior and a posterior longitudinal myotomy, disrupting the LES. More recently, the procedure has been modified and is limited to an anterior longitudinal myotomy.

After port placement, the laparoscopic Heller myotomy is performed by exposing the hiatus by placing gentle inferior and lateral retraction on the stomach. The phrenoesophageal fat pad is excised and the hiatus is exposed. The myotomy is then performed by splitting the muscular fibers of the LES, and exposing the bulging mucosa. Care is taken not to perforate the mucosa. Once the myotomy is created, it is carried proximally 5 to 6 cm and distally on to the stomach by 2 cm. Mucosal integrity is then checked by endoscopic insufflation. A Dor fundoplication (270-degree wrap) is added to control for postoperative reflux.[32]

Nearly 50 percent of patients develop GERD after a Heller myotomy.[32] Currently, most esophageal surgeons perform a partial wrap (Fig. 14-7) to control the symptoms of reflux. There is some debate regarding the type of wrap but a recent study showed that the Dor fundoplication is associated with good control of reflux symptoms and less dysphagia than a Nissen.[33,39]

## Outcomes

Several studies have demonstrated superiority of laparoscopic Heller myotomy when compared with botulinum toxin injection and pneumatic dilation. Myotomy provides long-term relief of dysphagia, chest pain, and regurgitation.

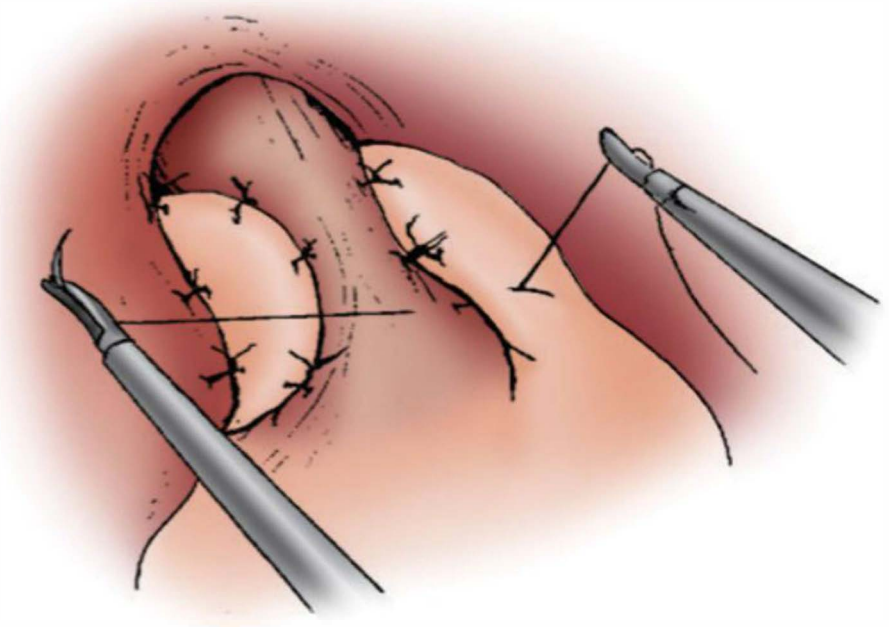


**FIGURE 14-7** Completed Toupet partial fundoplication. (From Smith CD. *Surg Gastrointest Endosc Clin N Am* 2009;19(1):35–48. With permission.)

Several authors believe that surgical myotomy should be the primary therapy for all patients who have achalasia.[30,31] Most recent series show excellent long-term relief of symptoms at 2 years. A study by Portale et al. reported on 113 patients who underwent Heller myotomy. They showed relief of symptoms at 2 years and greater than 90 percent probability of patients remaining asymptomatic at 5 years.[40,41]

## DIFFUSE ESOPHAGEAL SPASM

Diffuse esophageal spasm (DES) is a motility disorder of unknown etiology. It occurs in 3 to 5 percent of patients with esophageal motility disorders.[42] DES is characterized by simultaneous high-amplitude contractions associated with severe chest pain or dysphagia. There is no optimal treatment option for these patients, and the goal of therapy is to relieve symptoms and improve quality of life.

### Clinical Features and Workup

DES usually presents with severe chest pain. After cardiac causes have been ruled out, history reveals dysphagia or chronic pulmonary symptoms due to aspiration. Discerning the diagnosis may be difficult in this patient population, because up to 50 percent can have GERD. Similar to achalasia, DES patients should undergo endoscopy, esophagogram, and manometry. Esophagogram shows the classic appearance of the "corkscrew" esophagus (Fig. 14-5D). Manometry is the gold standard. DES is defined as simultaneous contractions in greater than 20 percent of wet swallows.[18] Manometry may also show long-duration contractions, high-amplitude waves, and spontaneous contractions not associated with swallows (Fig. 14-6B).

### Treatment

Since DES is rare, there is no clear treatment. Both medical and surgical options are available but without any evidence of their efficacy. Medical therapy includes smooth muscle relaxants including nitrates and calcium channel blockers. But many times these medical therapies are ineffective. There is some evidence for the use of antipsychotic and benzodiazepines, but there are no data supporting their use.[18]

Surgical options for DES include the creation of a long esophageal myotomy. A long esophageal myotomy is performed through a left thoracotomy or thoracoscopically.[43,44] Once access is gained, the esophagus is mobilized from the level of the aortic arch to the hiatus. A longitudinal incision is made, dividing the hypertrophied muscle from the arch to the hiatus. If the patient has evidence of a hypertensive LES, the myotomy is extended along the gastric wall, and a fundoplication is added to control reflux.[45]

Surgical outcomes for the long esophageal myotomy are good. A review of the surgical management of DES showed a decrease in symptoms from 50 to 86 percent, with no mortality and a low reintervention rate.[44] A more recent study looking at long esophageal myotomy in 20 patients found excellent outcomes; 90 percent had no dysphagia, and

100 percent were chest-pain free.[46] Overall, the outcomes are good, but the data are limited. Currently, there are no guidelines, but when patients have had failure of medical management, surgical options should be considered.

## NUTCRACKER ESOPHAGUS

Nutcracker esophagus was first described in 1978. As with DES, patients experience crushing chest pain and dysphagia. Esophagogram and endoscopy are usually normal in these patients. Manometry demonstrates high-amplitude contractions, greater than 180 mm Hg that may last up to 6 seconds.[18] Other manometric findings may include elevated LES pressures with normal relaxation and normal peristalsis (Fig. 14-6C). Treatment options for nutcracker esophagus are similar to DES, including pharmacotherapy and surgical intervention for patients who are refractory to medical management.

## ESOPHAGEAL DIVERTICULA

Esophageal diverticula are mucosal outpouchings of the esophagus. Diverticula are described on the basis of location and wall thickness. The majority of esophageal diverticula are acquired and develop secondary to esophageal motility disorders.[47] There are three types of diverticula based on location: Zenker's diverticulum located at the level of the cricopharyngeus, peribronchial diverticulum, and epiphrenic diverticulum. Of the three, Zenker's and epiphrenic diverticulum are pulsion diverticula that arise in areas of elevated intraesophageal pressures. The peribronchial diverticulum is a traction diverticulum, rarely seen today. Goals of treatment include restoration of normal motility and improvement of symptoms.

### Zenker's Diverticulum

#### PATHOPHYSIOLOGY

Zenker's diverticulum is located proximal to the UES on the posterior wall. The UES is composed of the inferior pharyngeal constrictors and the cricopharyngeus, the sling-like muscle completing the circumference of the cricoid cartilage.[48] There is an inherent area of weakness between these two muscles, allowing mucosa to protrude in response to elevated UES pressures and uncoordinated contraction of the pharynx and upper cervical esophagus.[49]

The physiologic function of the UES is based on the cricopharyngeus. It is composed of striated muscle and remains under tonic contraction due to vagal innervation. Inability of the cricopharyngeus to relax in response to a bolus of food results in elevated pressures. It is not clear why the cricopharyngeus fails, but pathologic examination of the cricopharyngeus has shown muscle fiber degeneration, necrosis, and fibroadipose tissue deposition.[50] These changes may lead to decreased elasticity of the muscle and restricted opening.

#### CLINICAL FEATURES

Zenker's occurs most commonly in the seventh and eighth decades of life. Prevalence is less than 1 percent in the general population.[49] Symptoms of a cricopharyngeal diverticulum include dysphagia and halitosis due to undigested food in the diverticulum. Other symptoms may include chronic cough, aspiration, and weight loss secondary to worsening dysphagia. The most striking clinical feature in patients with an enlarged diverticulum may be cervical borborygmi[49] or a gurgling noise when swallowing. If left untreated, there is a small risk of malignant degeneration of these pouches.[51]

#### DIAGNOSIS

As in all esophageal motility disorders, CXR, esophagogram, and endoscopy are required not only for diagnosis but to rule out additional pathology. The CXR for large diverticulum can be impressive. Air–fluid levels are seen on the lateral views within the pouch. Esophagogram is diagnostic, showing a large outpouching in the cervical esophagus.

#### TREATMENT

Treatment is indicated in all patients who have symptoms. Since most of these patients are elderly, comorbidities are the limiting factor in repair. Options for treatment include open myotomy, with or without resection of the diverticulum, diverticulopexy, and endoscopic treatment.

The traditional Zenker's repair is performed through the left neck. The proximal esophagus is identified medial and posterior to the anterior border of the sternocleidomastoid. The diverticulum is dissected to the base. The myotomy is performed in both directions, beginning at the base of the diverticulum. For smaller diverticula, it may be possible to leave the diverticulum in place, but for larger diverticula, diverticulectomy is preferred.[45] Other options include a diverticulopexy, in which the mouth of the diverticulum is tacked in a dependent fashion so that it drains and does not accumulate secretions.

Endoscopic treatment of a Zenker's diverticula is an alternative to the open approach. Under general anesthesia, a rigid endoscope is inserted. The septum and cricopharyngeal mask between the esophageal lumen and the Zenker's is identified. A cutting stapler is fired, transecting the septum and cricopharyngeal mask, creating a common channel between the two.[45] Current data suggest that endoscopic therapy of Zenker's results in improvement of symptoms with low complication rates.[49]

### Midesophageal Diverticula

Midesophageal diverticula are rare. Known as a traction diverticulum, periesophageal inflammation such as granulomatous disease results in full-thickness outpouching of the midesophagus. Patients occasionally present with symptoms of dysphagia and retrosternal chest pain. Barium esophagogram confirms the diagnosis of a small wide-mouthed

diverticulum. Excision of a traction diverticulum is rarely indicated since they are not symptomatic, and surgery is reserved for larger diverticulum.[52]

## Epiphrenic Diverticulum

Epiphrenic diverticula are mucosal outpouchings that occur within 10 cm of the distal esophagus.[53] These are pulsion diverticula that develop secondary to increased intraesophageal pressure usually associated with motility disorders.[54] Dysphagia, regurgitation, and heartburn are all common symptoms. Esophagography, endoscopy, and manometry identify the diverticulum as well as the underlying motility disorder. Seventy to one hundred percent of patients have an underlying motility disorder despite normal manometry.[47,54] In spite of normal manometry, a myotomy is still indicated.[53]

Treatment goals for epiphrenic diverticula are threefold: resection of the diverticulum, a long esophagomyotomy for treatment of the underlying motility disorder, and an antireflux procedure for the incompetent LES. Approaches include right or left thoracotomy and minimally invasive procedures. When comparing the approaches, open techniques have lower leak rates and similar morbidity to minimally invasive approaches. Most centers currently advocate an open approach and minimally invasive surgery in centers with experience.[54]

## Benign Esophageal Strictures

Benign esophageal strictures are a common cause of dysphagia in patients. The most common cause is peptic stricture and accounts for 60 to 70 percent of cases.[55] Other etiologies include Schatzki rings, caustic ingestion, radiation therapy, or anastomotic strictures. Strictures can be classified according to their complexity. Most simple strictures are short, focal, and straight and allow a normal endoscope to pass easily; others are more complex. Long (>2 cm), angulated, or severely narrowed strictures are termed complex strictures.[55] Although simple strictures are amenable to one to three dilations, complex strictures are more difficult to treat.[56]

## Treatment

Treatment is directed toward relief of dysphagia. Options include dilation, medical therapy, stenting, and in refractory cases, surgery (Fig. 14-8). Dilators vary; mechanical dilators such as the

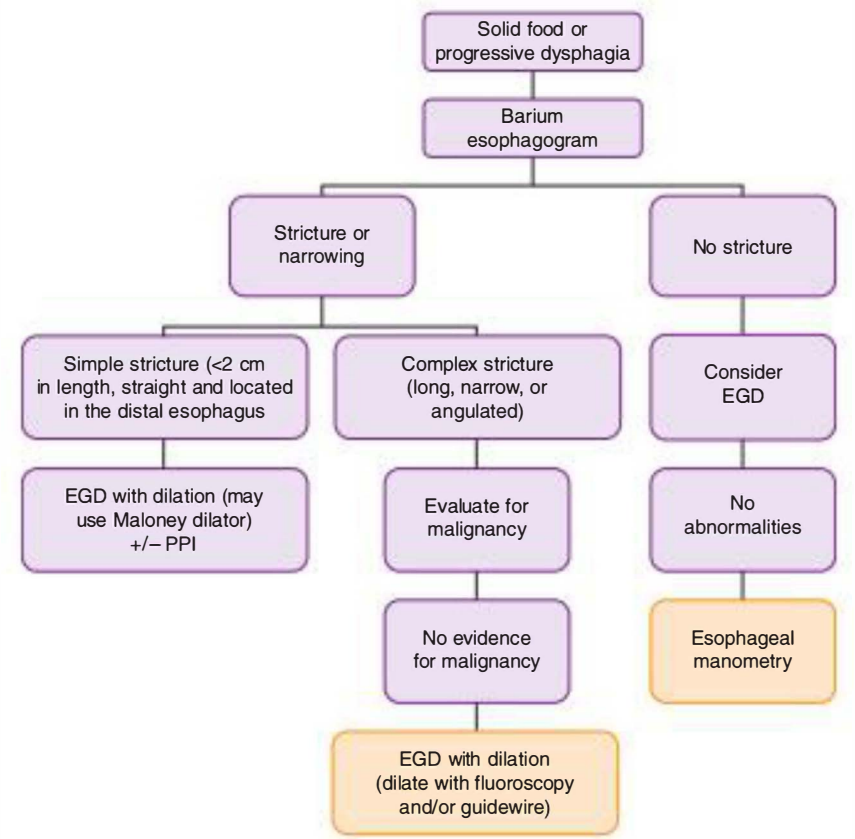



**FIGURE 14-8** Management algorithm for benign esophageal stricture. (From Ferguson DD. Evaluation and management of benign esophageal strictures. *Dis Esophagus* 2005;18(6):359–364. With permission.)

Maloney or Savary dilator can be passed without the use of a guidewire. In comparison, balloon dilators are passed over a wire and are insufflated under direct vision. Complications include perforation, hemorrhage, and bacteremia.[56] To minimize the risk of complications, the "rule of three"[57] should be applied. Dilators should be passed no more than three times through the stricture, and the diameter of the esophagus should not be increased by any more than 2 to 3 mm.[57] Overall, dilation of benign esophageal strictures is safe with minimal morbidity, but outcomes are variable and may require further treatment.

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## GASTROESOPHAGEAL REFLUX DISEASE AND ESOPHAGEAL MOTILITY DISORDERS BOARD REVIEW QUESTIONS (CHAPTER 14)

1. Which is correct regarding manometry for the diagnosis of achalasia?
   A. Normal peristalsis, with contraction amplitude >2 standard deviations above normal and greater than 180 mm Hg in distal esophagus with contractions greater than 6 seconds.
   B. Hypertensive LES with resting pressure >45 mm Hg, incomplete relaxation of the LES with swallowing, residual pressure of >8 mm Hg, and esophageal aperistalsis.
   C. Simultaneous contractions in greater than 20 percent of wet swallows and occasionally long-duration contractions, high-amplitude waves, and spontaneous contractions not associated with swallows.
   D. Hypertensive LES with resting pressure >45 mm Hg, incomplete relaxation of the LES with swallowing, residual pressure of >8 mm Hg, and esophageal peristalsis.
   E. Hypotensive LES, absence of LES relaxation with swallowing, and residual pressure >15 mm Hg.

2. A 60-year-old woman presents to your office with long-standing dysphagia. She has complaints of difficulty swallowing solids and occasionally liquids. A barium esophagogram is performed and is consistent with her diagnosis. What would be the expected findings on endoscopy?
   A. Normal esophageal mucosa
   B. Tongues of red mucosa, projecting proximally along the mucosal surface
   C. Retained food and saliva with esophagitis secondary to stasis
   D. Edematous, friable walls which are easily perforated
   E. Stricture at the upper esophageal sphincter

3. All of the below are implicated in LES dysfunction except:
   A. Recumbent position
   B. Intra-abdominal length of the LES
   C. Dilation of the diaphragmatic crus secondary to a hiatal hernia
   D. Esophageal motility
   E. Gastric distension

4. Which of the following is not an indication for surgery in GERD?
   A. Failure to respond to or inability to tolerate PPI therapy
   B. Patients who are symptomatic after 3 months of medical therapy
   C. A large hiatal hernia
   D. Barrett's with high-grade dysplasia
   E. Severe esophagitis

5. Laparoscopic Nissen fundoplication is associated with the following except:
   A. Shorter hospital stay
   B. Improved control of reflux symptoms and dysphagia
   C. More rapid return to work
   D. Less postoperative pain
   E. Lower total cost

## ANSWERS

1. **Answer: B.** Characteristic findings of achalasia on manometry are a hypertensive LES with resting pressure >45 mm Hg, incomplete relaxation of the LES with swallowing, residual pressure of >8 mm Hg, and esophageal aperistalsis.
2. **Answer: C.** This patient has poor esophageal function and the anticipated endoscopic findings would be stasis with subsequent retained food and saliva, and underlying esophagitis.
3. **Answer: A.** The recumbent position is not associated with LES dysfunction. A shortened intra-abdominal length of the LES, dilation of the diaphragmatic crus, decreased esophageal motility, and gastric distension are all associated with LES dysfunction.
4. **Answer: D.** The presence of Barrett's disease alone is not an indication for surgical intervention. Failure to respond to PPI therapy, continued symptoms on adequate medical therapy, a large hiatal hernia, and severe esophagitis are indications for surgery.
5. **Answer: B.** Laparoscopic Nissen fundoplication has equivalent control of reflux symptoms and dysphagia compared to open Nissen fundoplication. The laparoscopic approach is associated with shorter hospitalization, lower cost, more rapid return to work, and less postoperative pain.

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# 15 Esophageal Perforation

*Clinton D. Kemp*
*Stephen C. Yang*

**KEY CONCEPTS**

- Epidemiology
  - Iatrogenic instrumentation (e.g., endoscopy, dilatation, tube passage, etc.) has replaced spontaneous rupture as the leading cause of esophageal perforation and accounts for 60 to 75 percent of esophageal injuries.
- Pathophysiology
  - Esophageal perforation results in leakage of esophageal and gastric contents into the mediastinum, producing a chemical burn and superinfection. Left untreated, this leads to a severe inflammatory response and sepsis.
  - Esophageal perforations are broadly divided into intraluminal and extraluminal types. Intraluminal injuries are caused by instrumentation, foreign bodies, caustic ingestion, esophagitis, carcinoma, infection, or barotrauma. Extraluminal causes include stab or gunshot wounds, blunt trauma, and operative injuries.
- Clinical features
  - Patients sustaining a cervical esophageal perforation typically present with cervical pain, odynophagia, subcutaneous emphysema, and neck tenderness and crepitus. Dysphagia, pain, tachycardia, and fever usually occur shortly after iatrogenic perforation. Intra-abdominal esophageal perforation usually presents with peritonitis. Late manifestations of untreated perforations often include hypoxia, sepsis, and shock.
- Diagnostics
  - An antecedent history of instrumentation or vomiting often points to the etiology and possibility of esophageal perforation. Plain chest radiography may show pneumomediastinum, subcutaneous emphysema, or subdiaphragmatic air. Diagnosis is usually confirmed with esophagography, which demonstrates a leak in 50 to 60 percent of cervical and 80 to 90 percent of thoracic esophageal perforations. Esophagoscopy and computed tomography are other diagnostic modalities used in selected circumstances.
- Treatment
  - The initial management of patients presenting with esophageal perforations includes cessation of oral intake, fluid resuscitation, and broad-spectrum antibiotics. Definitive treatment of perforations is divided into nonoperative and operative management. Nonoperative management may be undertaken in selected patients with limited perforations that drain back into the esophagus and are not associated with distal obstruction, communication with the abdominal cavity, or systemic sepsis. Operative treatment is predicated on adequate debridement, reinforced primary repair, wide drainage, and distal feeding tube placement. In the absence of underlying esophageal disease, there is a trend toward primary reinforced repair, regardless of the perforation's duration. Underlying esophageal disease is best addressed before or at the time of perforation repair.
- Outcomes
  - Esophageal perforation has an associated mortality rate of 20 percent.

## INTRODUCTION

Esophageal perforation was first described in 1724 by the Dutch physician Hermann Boerhaave, who published the presentation, clinical course, and autopsy findings of spontaneous rupture of the esophagus in his patient Lord van Wassenaer, High Admiral of the Dutch Navy. In this seminal work, he described the clinicopathologic correlation between esophageal perforation and a fatal outcome, one that remained inevitable for over 200 years. Despite modern surgical techniques, perforation of the esophagus still represents a true surgical emergency. In the mid-20th century, successful primary repair of esophageal perforation was first reported by Barrett in 1946 and later by Olsen and Claggett in 1947, and esophagectomy for esophageal perforation was described by Satinski and Kron in 1952, all of which led the

way to the modern treatment of these injuries.[1-4] Although spontaneous esophageal rupture is uncommon today, the dramatic increase in the use of invasive procedures for the diagnosis and treatment of gastrointestinal diseases has resulted in a significant increase in the incidence of esophageal perforation.

## PATHOPHYSIOLOGY

The esophagus is prone to rupture by various mechanisms due to the lack of an enveloping serosal layer. As a consequence of its location, perforation of the esophagus can rapidly develop into a fatal disease process unless a prompt diagnosis is made and proper treatment is initiated immediately. Following perforation, the negative intrathoracic pressure pulls esophageal and gastric contents into the mediastinum. Oral bacteria present in saliva as well as digestive enzymes, acidic gastric secretions, and bile produce a chemical burn that can lead to a necrotizing superinfection of adjacent mediastinal and upper abdominal organs. This combination of insults leads to a severe local inflammatory response and if left untreated, eventually develops into systemic sepsis.

## CLINICAL FEATURES

### Epidemiology

The incidence of esophageal perforation in the United States is estimated to be 3 per 100,000 people.[5] The most common location for perforation is in the intrathoracic esophagus (54 percent), followed by the cervical esophagus (27 percent) and intra-abdominal esophagus (19 percent).[5] A recently published analysis of modern series of over 500 patients with esophageal perforations identified iatrogenic injuries as the most common cause of esophageal perforation (59 percent), followed by spontaneous perforation (15 percent), ingestion of foreign bodies (12 percent), trauma (9 percent), operative injuries (2 percent), malignancy (1 percent), and other causes (2 percent).[6] A relationship between cause and location exists (Fig. 15-1).

### Etiology

Perforation of the esophagus can be divided into intraluminal or extraluminal causes.

#### INTRALUMINAL CAUSES

***Instrumental Injuries.*** Iatrogenic perforations account for the majority of esophageal perforations and can occur during routine diagnostic endoscopy, therapeutic dilatation, stent placement, enteral tube passage, or endoscopic ultrasound or echocardiography. The actual risk of perforation during routine endoscopy alone is quite low and is estimated to be 0.11 percent with traditional rigid esophagoscopes and even lower (0.03 percent) with modern flexible endoscopes.[6] Nevertheless, the risk of perforation increases considerably with therapeutic intervention and ranges from 0.3 percent after balloon dilatation to 25 percent after palliative stent placement for malignancy.[7,8] In the absence of a diseased esophagus, iatrogenic injuries occur most commonly in Killian's triangle, which is formed by the inferior pharyngeal constrictor and the cricopharyngeus muscles, but perforation of the esophagus also occurs at areas of normal anatomic narrowing, such as the distal esophagus just proximal to the gastroesophageal junction and the impingement of the aortic arch and left mainstem bronchus.[9]

***Foreign Bodies.*** Nearly all objects (80–90 percent), especially those less than 2 cm in size, will typically be able to

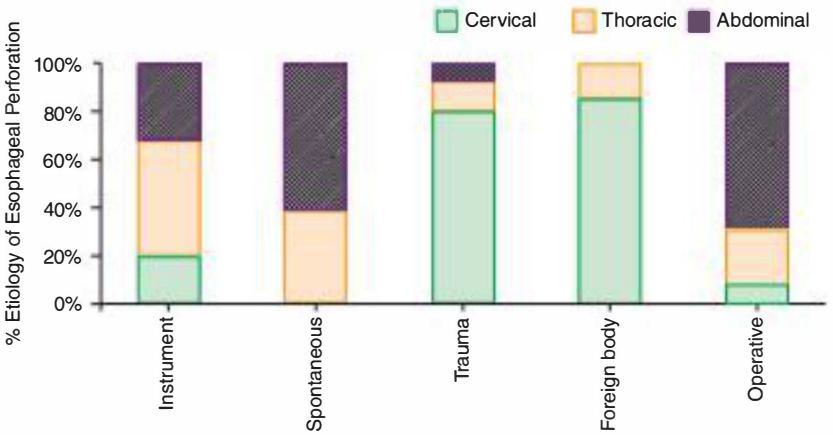



**FIGURE 15-1** Relationship of cause with anatomic location of esophageal perforation. (Adapted with permission from Brinster et al. Evolving options in the management of esophageal perforation. *Ann Thorac Surg* 2004;77:1475–1483. Copyright Elsevier.)

pass through a nonpathologic esophagus and the remainder of the gastrointestinal tract without difficulties.[10,11] Objects with sharper edges (e.g., chicken or fish bones, nails, razor blades, safety pins, etc.), or those of larger size (e.g., coins) can, however, cause acute perforation in areas of anatomic esophageal narrowing. This occurrence is more common in children and those with concomitant psychiatric illness, and is often associated with a delay in diagnosis that can lead to the development of mediastinal abscess or empyema.

***Chemically Induced Perforation.*** Prior to the widespread availability of proton pump inhibitors, reflux esophagitis with esophageal ulcer was a relatively common cause of esophageal perforation. Currently, reflux disease alone rarely leads to perforation of the esophagus. Today, ingestion of caustic alkaline or acidic materials is the most common form of chemical injury and often occurs intentionally by suicidal adults or accidentally by young children. Severity of injury is dependent on both the type and the concentration of the caustic agent as well as the length of time in contact with the esophageal mucosa.[12] Severe chemical insults resulting in perforation typically occur several days after ingestion, following necrosis and as the injured esophagus attempts repair of the damage from the offending agent.[13] Chemical damage with subsequent perforation following the retention of pills in the esophagus and delayed entry into the stomach has been reported for various pharmaceutical agents such as aspirin/NSAIDs, bisphosphonates, and antibiotics/antivirals.[14]

***Esophageal Carcinoma.*** Perforation in patients with esophageal cancer is typically secondary to instrumentation, but can also occur spontaneously with locally advanced tumors. The prognosis of these patients is grim and mortality from this condition approaches 50 percent.[15]

***Infection.*** Severe esophageal infections with human immunodeficiency virus (HIV), herpes simplex virus (HSV), cytomegalovirus (CMV) *Candida* species, and tuberculosis, typically in immunocompromised patients, all have been reported to cause esophageal perforation.[16]

***Spontaneous Perforation (Boerhaave Syndrome and Barotraumas).*** Perforation of the esophagus may be related to a rapid increase in intraluminal pressure (e.g., emesis, coughing, weight lifting, seizures). If the upper esophageal sphincter fails to relax, the increase in intra-abdominal pressure may lead to a tremendous pressure rise within the esophagus, resulting in perforation. When the perforation due to a rise in intra-abdominal pressure is postemetic in nature, the condition is known as Boerhaave syndrome and typically occurs in the distal third of the esophagus on the left.[17]

### EXTRALUMINAL CAUSES

***Traumatic Injuries.*** Esophageal perforation from penetrating thoracic trauma typically involves the cervical esophagus and is rarely fatal by itself.[18] Esophageal perforation secondary to blunt trauma is rare, but can occur secondary to compression of the esophagus between the sternum and spine in motor vehicle accident.[19]

***Operative Injuries.*** Perforation of the esophagus has been reported with pulmonary resections, atrial operations, thoracic aortic aneurysm repair, mediastinoscopy, operations on the anterior cervical spine, laparoscopic fundoplication or myotomy procedures, and even thyroid surgery.[6]

## CLINICAL PRESENTATION

The diagnosis of esophageal perforation may be suspected from the patient's clinical history as often an antecedent episode of vomiting, or recent instrumentation can be elicited from patients with esophageal perforation. The clinical presentation of esophageal perforation depends on three factors: location, degree of containment, and time elapsed since injury. The differential diagnosis includes myocardial infarction, peptic ulcer disease, pancreatitis, aortic dissection, spontaneous pneumothorax, and pneumonia.

Physical examination findings may include fever, tachycardia, hypotension, tachypnea, and other end-organ manifestations of sepsis. Local tenderness is associated with an upper esophageal perforation and peritonitis with an abdominal esophageal perforation. There may be crepitus present. Among patients with esophageal injuries, pain is the most frequently reported symptom (71 percent), followed by fever (51 percent), dyspnea (24 percent), and crepitus (22 percent).[20] The classical association of vomiting, lower chest pain, and subcutaneous emphysema (Mackler triad) is only found in half of the patients with esophageal perforation.[21]

Cervical perforation typically presents with cervical pain, odynophagia, and subcutaneous emphysema with neck tenderness and crepitus on palpation. Iatrogenic perforation usually presents shortly after the procedure, with dysphagia, pain, tachycardia, and fever. If left untreated, this progresses to hypoxia, sepsis, and shock. Spontaneous esophageal rupture or Boerhaave syndrome occurs more commonly outside the hospital setting. The typical patient is an elderly male with a history of recent emesis. These patients tend to present late and have a worse prognosis. Intra-abdominal perforations usually present with abdominal tenderness or frank peritonitis and rapidly deteriorate into septic shock.

## DIAGNOSTIC MODALITIES

Evidence of esophageal perforation is present on 90 percent of plain-film radiographs, and findings include pneumomediastinum, subcutaneous emphysema, hydrothorax, pneumothorax, or hydropneumothorax, and subdiaphragmatic air.[22] These findings may not be present early after injury.

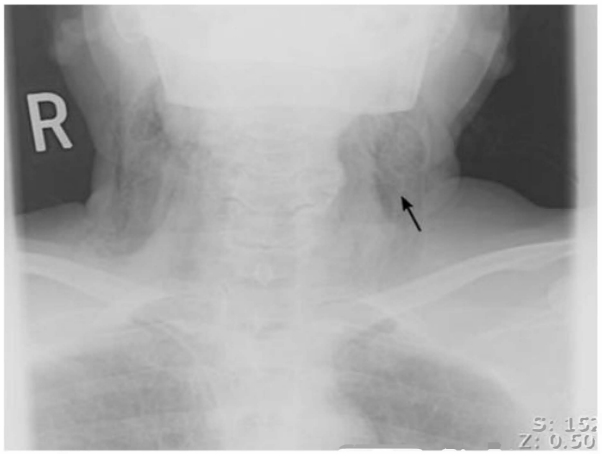



FIGURE 15-2 Anteroposterior view of neck radiograph. The arrow points to subcutaneous air.

The diagnosis is usually confirmed with an esophagogram with water-soluble (e.g., Gastrografin) contrast, which will demonstrate the leak in 50 percent of cervical and 75 to 80 percent of thoracic perforations (Figs. 15-2 to 15-4).[23] If there is no demonstration of extravasation of water-soluble contrast and the suspicion of esophageal perforation remains high, an esophagram with thin barium contrast should be performed as nearly one-quarter of patients with a negative Gastrografin esophagram are found to have a positive barium swallow study.[5] Barium has been shown to be able to detect up to 60 percent of cervical and up to 90 percent of intrathoracic esophageal perforations.[6] Such studies should be performed with the patient in the right lateral decubitus position so as to avoid rapid transit of contrast into the stomach, in which case a small leak may be missed. Esophagrams may have to be repeated in the face of negative Gastrografin and barium studies if the diagnosis of esophageal perforation remains likely.



FIGURE 15-3 Lateral view of Gastrografin contrast study. The arrow points to contrast extravasation in the midesophagus.

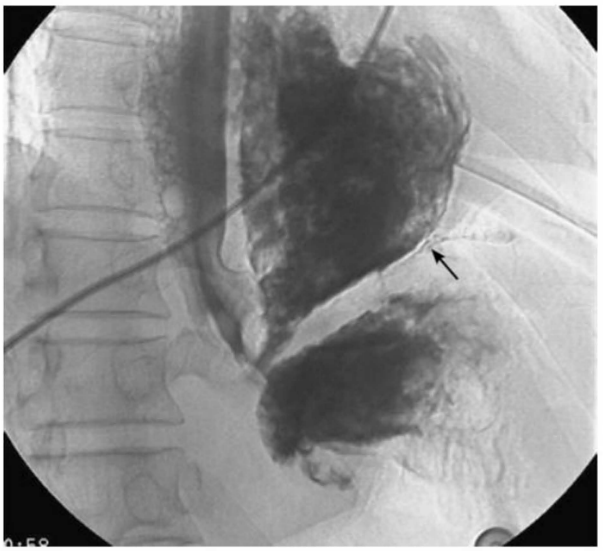


FIGURE 15-4 Lateral view of Gastrografin contrast study. The arrow points to contrast extravasation in the distal esophagus at the gastroesophageal junction.

Esophagoscopy without insufflation is the diagnostic option in unstable or mechanically ventilated patients and has a sensitivity of 100 percent and specificity of 83 percent for detecting perforation.[24] Any discoloration or submucosal hematoma on upper endoscopy should be considered highly suspicious for perforation.

Computed tomography (CT) of the chest and abdomen is useful in selected patients when esophagography is unavailable or the findings from such studies are nondiagnostic. CT is particularly useful after the perforation has sealed and may help direct percutaneous, catheter-based drainage of any fluid collections. Abnormalities on chest CT may include mediastinal free air, esophageal thickening, or an air–fluid level adjacent to the esophagus, representing a mediastinal abscess cavity.[25,26]

## THERAPY

The overriding consideration in the treatment of esophageal perforation is the status of the native (preperforation) esophagus and, in particular, the presence of cancer, achalasia, or

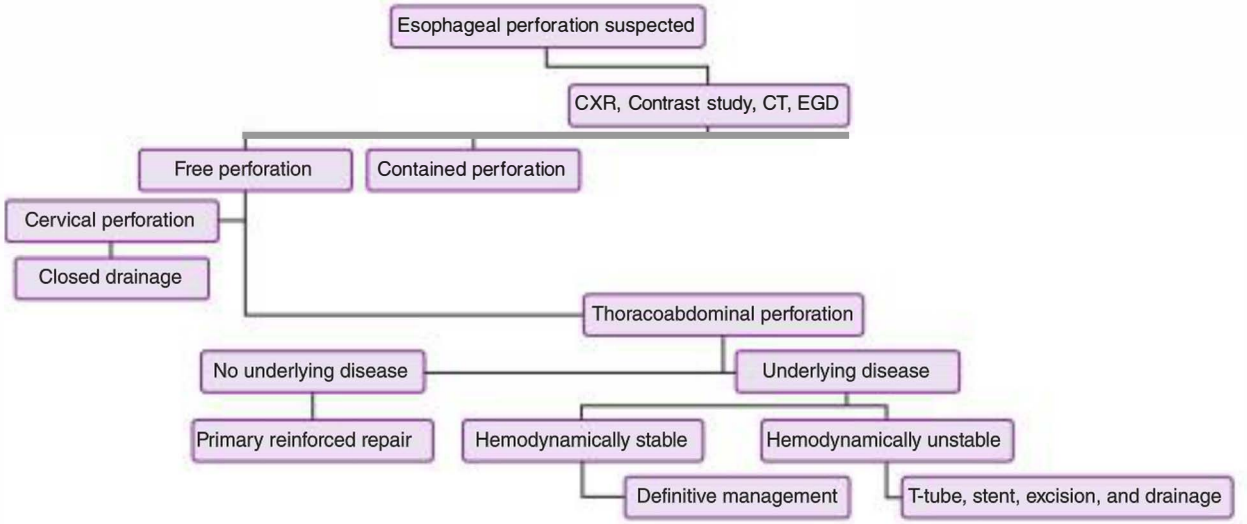



**FIGURE 15-5** Decision-making flowchart. An algorithm outlining the current management of esophageal perforation.

stricture.[27] Other considerations include contained versus free leak, the patient's clinical status, time since perforation, and location of the perforation. The treatment principles are based on (1) debridement of necrotic tissues to control infection and prevent continued soilage, (2) elimination of any distal esophageal obstruction, (3) secure closure of the perforation with appropriate drainage, and (4) establishment of enteral access. Treatment options are operative and nonoperative, and an algorithm outlining the current management of esophageal perforation is shown in the decision-making flowchart (Fig. 15-5).

## Nonoperative Management

In 1979, Cameron published the criteria for nonoperative management of esophageal perforation with a delay in diagnosis, which were updated by Altorjay in 1997.[28,29] These criteria include (1) intraluminal dissection, (2) transmural perforation that drains back into the esophagus, (3) no associated obstruction in the distal esophagus, (4) no perforation within the abdominal cavity, and (5) no evidence of systemic sepsis. More recently, Abbas et al. created an esophageal perforation severity score based on clinical data at the time of presentation (Fig. 15-6).[30] Up to 18 points are given as follows: 1 point each for age >75 years, tachycardia >100 beats per minute, leukocytosis >10,000 WBC/mL, or pleural effusion, 2 points each for fever >38.5°C, noncontained leak, or respiratory compromise (tachypnea >30 beats per minute or mechanical ventilation), time to diagnosis >24 hours, and 3 points each for cancer or hypotension, for a total of 18 points. A retrospective analysis of 119 patients using this scoring system revealed a correlation between morbidity and mortality and esophageal perforation severity scores. Those patients with lower severity scores had shorter hospital stays, fewer complications, and lower mortality, and those patients successfully treated with nonoperative management had lower clinical score than those who underwent operative intervention.[30]

**Esophageal perforation severity score**

| Variable | Score (range 1–3) |
|---|---|
| Age >75 years | 1 |
| Tachycardia >100 beats/min | 1 |
| Leukocytosis >10,000 WBC/ml | 1 |
| Pleural effusion (on CXR or CT) | 1 |
| Fever >38.5°C | 2 |
| Noncontained leak (on CT or barium swallow) | 2 |
| Respiratory compromise (respiratory rate >30, mechanical ventialtion) | 2 |
| Time to diagnosis >24 h | 2 |
| Cancer | 3 |
| Hypotension | 3 |
| **Total potential score** | **18** |

CT, computed tomography; CXR, chest x-ray, white blood cell.

**Outcomes of patients with esphageal perforation based on a perforation score (0–18)**

| | Clinical score | | |
|---|---|---|---|
| | ≤2 ($n$ = 44) | 3–5 ($n$ = 49) | >5 ($n$ = 26) |
| Complication rate (%) | 53 | 65 | 81 |
| Mortality (%) | 2 | 6 | 27 |
| Length of stay (days) | 10 | 16 | 28 |

**FIGURE 15-6** Esophageal perforation severity score and association with clinical outcome. (Adapted with permission from Abbas G, Schuchert MJ, Pettiford BL, et al. Contemporaneous management of esophageal perforation. *Surgery* 2009;146:749–755. Copyright Elsevier.)

Common to all types of perforation, once esophageal perforation is suspected, oral intake is stopped, fluid resuscitation is instituted, and broad-spectrum antibiotics are initiated. Acid secretion is reduced with proton pump inhibitors, and patients are sustained on total parenteral nutrition. Mediastinal and pleural collections should be drained via tube thoracostomy or by percutaneous catheters placed under CT guidance. The importance of continued monitoring for any clinical deterioration cannot be overemphasized as operative intervention should be performed immediately on any such clinical changes.

## Operative Management

### PERFORATION OF THE CERVICAL ESOPHAGUS

Perforation of the cervical esophagus is usually treated nonoperatively with complete cessation of oral intake, institution of broad-spectrum antibiotics, and frequent oral suctioning.[20]

Subsequent development of an abscess above the aortic arch, however, can be managed with drainage alone through a cervical approach. An incision is made along the anterior border of the left sternocleidomastoid muscle. The omohyoid and strap muscles are divided. The carotid sheath is identified and mobilized laterally, and the inferior thyroid artery is ligated. The recurrent laryngeal nerve can be found as it courses into the tracheoesophageal groove, just anterior to the inferior thyroid artery. The esophagus is identified and a search is made for the site of perforation. Closure of the perforation is not mandatory, especially when severe inflammation is present and there is no distal obstruction; however, closure of an accessible early perforation may be carried out provided that minimal dissection is performed. In such repairs, the esophageal mucosa is approximated with interrupted fine absorbable sutures and the muscle layer closed separately. An associated mediastinal abscess can often be drained by blunt dissection through the thoracic inlet down into the abscess. Placement of a closed suction drain in the abscess cavity and closing the wound complete the procedure. Regardless of whether simple drainage or surgical closure is used for cervical perforations, most patients recover promptly and have a low mortality rate. A repeat swallow study is necessary prior to resuming oral intake.

### INTRATHORACIC AND ABDOMINAL ESOPHAGEAL PERFORATION

The mortality rates of intrathoracic esophageal perforation are almost three times those of cervical esophageal injuries.[31] The most favorable outcomes are obtained after primary repair of such perforations within 24 hours. However, accumulating experience suggests that, regardless of the duration of the injury, primary repair should be attempted in patients without an underlying abnormality of the esophagus and with stable hemodynamics.[32] Perforations of the middle third of the esophagus are best approached through a right thoracotomy, whereas a left thoracotomy is best for perforations of the lower esophagus. Perforations should be approached on the side of pleural contamination. Abdominal esophageal perforation without significant intrapleural contamination may be approached through an upper midline incision.

After surgical exposure has been gained, contaminated fluid is drained and mediastinal and esophageal devitalized tissues are debrided. Next, the location of the perforation is sought. When this has been identified, exposure is facilitated by incising the muscle layers proximally and distally. Once well exposed, the mucosal defect is trimmed and closed using interrupted fine monofilament absorbable suture. Subsequently, the muscle layer is approximated over the mucosal closure. It is important to buttress the repair with adjacent tissues to reduce the rate of leak. The choice of buttressing tissue depends on the approach used for the repair. During a thoracic approach, a pleural intercostal muscle or an elevated diaphragmatic pedicle flap can be used to bolster the primary repair.[33,34] Wide mediastinal drainage is mandatory in addition to the repair. Drainage is achieved by opening the mediastinal pleura above and below the level of the tear from the thoracic inlet to the diaphragm and then irrigating and draining the mediastinum with well-positioned chest tubes and drains. If a laparotomy is performed for perforation of the lower esophagus, the repair can be reinforced with omentum or a fundoplication.[35]

### LATE ESOPHAGEAL PERFORATION

Esophageal perforation with a delayed presentation or diagnosis results in increased mediastinal contamination, inflammation, tissue destruction, and hemodynamic instability. In the absence of underlying esophageal disease, many believe that a primary reinforced repair is the procedure of choice regardless of the perforation's duration. Drainage alone is acceptable in selected cases of cervical perforations. Unstable patients represent a unique challenge and are best served with either resection, control of the esophageal fistula with a T tube and wide pleural drainage, or endoscopic placement of a removable self-expandable Silastic stent and drainage. Esophageal exclusion and diversion is rarely necessary or appropriate with the number of options currently available.

### ESOPHAGEAL PERFORATION ASSOCIATED WITH ESOPHAGEAL DISEASES

Primary repair is ill advised in the presence of preexisting esophageal disease such as cancer or stricture, since the underlying process remains and is associated with a high likelihood of repair breakdown and subsequent mortality.[36,37] In most circumstances, the best option for distal malignant obstruction is resection with delayed reconstruction.[38] In selected patients with an early diagnosis of esophageal

perforation and minimal pleural and mediastinal contamination, gastrointestinal continuity may be reestablished at the time of the primary resection.[38,39]

Patients with achalasia who develop a perforation during balloon dilatation should undergo mucosal closure of the perforation with closure of the overlying muscle, followed by a complete myotomy on the opposite side of the esophagus.[40] The repair is buttressed with a partial fundoplication.

When perforation occurs in the presence of severe gastroesophageal reflux, an antireflux procedure is indicated both to buttress the repair and to treat the reflux. In the setting of severe caustic injuries, primary repair is rarely undertaken. The injured esophagus and/or stomach are resected through a transhiatal approach. The esophageal hiatus is closed to avoid herniation of intra-abdominal organs into the chest. The contaminated chest is drained, and a gastrostomy or feeding jejunostomy tube is placed. Patients are returned to the operating room at a later date for definitive reconstruction.

## OUTCOMES

Meta-analyses of patients with esophageal perforations from 1980–1990 to 1990–2003 have demonstrated an overall mortality of 18 to 22 percent in the modern era.[6,41] Several factors have been found to influence outcomes following esophageal perforation, including etiology, anatomic location, and time to repair. According to etiology, spontaneous perforation has the highest average mortality of 36 percent (range 0–72 percent), followed by iatrogenic perforation 19 percent (7–33 percent), and traumatic perforation 7 percent (0–33 percent).[6] By anatomic location, thoracic esophageal perforation has the highest average mortality of 27 percent (0–44 percent), followed by abdominal esophageal perforation 21 percent (0–43 percent), and cervical 6 percent (0–16 percent).[6] Time to repair is also important; mortality rates for those repaired within 24 hours of injury have the lowest mortality of 25 percent, which rises to 65 percent for those repaired from 24 to 48 hours after injury, and 75 to 89 percent after 48 hours following perforation.[6]

## SUMMARY

Esophageal perforation continues to pose a diagnostic and therapeutic challenge and has an associated mortality rate of approximately 20 percent. Instrumentation has replaced spontaneous rupture as the leading cause of esophageal perforation. Nonoperative management is appropriate in selected patients, but patients with evidence of systemic illness require prompt intervention. In the absence of cancer or an undilatable stricture, reinforced primary repair is the preferred treatment for patients who require an operation. Selection of treatment must be individualized and take into account many variables, including cause, duration, underlying esophageal disease, and the patient's condition.

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## ESOPHAGEAL PERFORATION BOARD REVIEW QUESTIONS (CHAPTER 15)

1. Which of the following is correct regarding esophageal injury?
   A. Trauma is the most common cause for esophageal rupture.
   B. With modern techniques, instrumentation injuries have been eliminated.
   C. The thoracic esophagus is the most common location for esophageal rupture.
   D. Cervical perforations are a common complication of difficult esophageal intubation.
   E. Insufflation should be avoided during evaluation of an obstructive lesion.

2. Which is correct regarding instrumental injury of the esophagus?
   A. Instrumentation causes over 50 percent of all esophageal perforations.
   B. In the absence of esophageal pathology, the most common site for iatrogenic injuries is the GE junction.
   C. Perforation rarely occurs at Killian's triangle.
   D. Rigid endoscopy has minimized iatrogenic perforation.
   E. Stent placement for malignancy is associated with a perforation rate of 5 percent.

3. Which of the following is true concerning the diagnosis of esophageal perforation?
   A. Thin barium contrast should be used for initial swallow studies.
   B. CT scanning is the modality of choice in an unstable or mechanically ventilated patient.
   C. Pleural effusion is a late finding on chest imaging.
   D. Water-soluble contrast will demonstrate intrathoracic leak in over 90 percent of patients.
   E. Esophagoscopy has a low sensitivity and specificity for perforation.

4. Which is true regarding the surgical approach for esophageal perforation?
   A. Perforations of the middle third of the esophagus are best approached through a left thoracotomy.
   B. Perforations should be approached on the side of pleural contamination.
   C. Perforations above the aortic arch are best approached through a right-neck incision.
   D. Conservative therapy is acceptable if there is extraluminal dissection.
   E. Closure of the perforation is mandatory.

5. Which is correct regarding treatment of an esophageal perforation in the presence of concomitant esophageal disease?
   A. Patients with achalasia should undergo mucosal closure of the perforation, closure of the overlying muscle, complete myotomy on the opposite side, and partial fundoplication.
   B. An antireflux procedure is not indicated in the setting of severe GERD.
   C. Primary repair is preferred in the presence of stricture.
   D. Formal esophageal resection should be performed for associated squamous cell carcinoma.
   E. Primary repair is indicated in a severe caustic injury to preserve esophageal length.

## ANSWERS

1. **Answer: C.** The thoracic esophagus is the most common location for esophageal rupture. Esophageal rupture after trauma is rare. Instrumentation injuries have increased due to more aggressive use of balloon dilation and esophageal stenting. Cervical perforation is rare during difficult esophageal intubation. Insufflation is necessary for thorough evaluation of an obstructive lesion.
2. **Answer: A.** Instrumentation is the cause of about 59 percent of all esophageal perforations. The most common site of iatrogenic injury is Killian's triangle in the cervical esophagus. Rigid endoscopy has a higher rate of iatrogenic injury compared with flexible endoscopy, and stent placement for malignancy is associated with a 25 percent perforation rate.
3. **Answer: C.** Pleural effusion is a late finding on chest imaging. Water-soluble contrast should be used for initial swallow studies, but will only demonstrate in the leak in 50 to 80 percent of patients. CT scanning is best reserved for patients after the perforation is sealed.

Esophagoscopy has a high sensitivity and specificity for detection of perforation.

4. **Answer: B.** Perforations should be approached on the side of pleural contamination. Perforations of the middle third are best approached through a right thoracotomy. Perforations above the aortic arch are managed with a left-neck incision. Conservative therapy is not indicated if there is extraluminal dissection. Closure of the perforation is not mandatory if there is adequate drainage.
5. **Answer: A.** Patients with achalasia should undergo mucosal closure of the perforation, closure of the overlying muscle, complete myotomy on the opposite side, and partial fundoplication. An antireflux procedure is indicated in the setting of severe GERD. Primary repair is not indicated for stricture or caustic injury, as the repair has a high likelihood of breakdown and mortality. Delayed reconstruction is preferred for patients with malignancy.

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# 16 Esophageal Cancer

*Jules Lin*
*Mark B. Orringer*

**KEY CONCEPTS**

- Epidemiology
  - Esophageal adenocarcinoma is the fastest growing solid malignancy in the United States.
- Pathophysiology
  - Barrett metaplasia is the precursor lesion to esophageal adenocarcinoma.
- Clinical feature
  - Most patients presenting with symptoms already have systemic disease.
- Diagnostic
  - In selecting the optimal treatment, endoscopic ultrasound is an important tool in determining the depth of invasion and regional nodal involvement.
- Treatment
  - Neoadjuvant chemoradiation may improve survival particularly in patients with a complete pathologic response.
- Prognosis
  - The stage at diagnosis is the most important prognostic factor.

## INTRODUCTION

The incidence of esophageal cancer in the United States is approximately 13,000 cases per year. Adenocarcinoma of the esophagus (EAC) is the fastest growing solid malignancy, and it is now more frequent than esophageal squamous cell carcinoma (ESCC) in the United States. Although resection offers the best chance for cure, most patients who present with symptoms already have systemic disease and are incurable. The most important prognostic factor for esophageal cancer remains the stage of disease at the time of diagnosis. Currently, the best strategy for improving survival is early diagnosis followed by resection. Neoadjuvant chemoradiation is being used increasingly in the treatment of locally advanced disease. However, despite improvements in operative technique and postoperative care, the overall 5-year survival remains less than 15 percent, highlighting the need for novel diagnostic and treatment modalities.

## Pathophysiology

### ESOPHAGEAL SQUAMOUS CELL CARCINOMA

Nutritional deficiencies, including low levels of vitamins A, C, and riboflavin as well as minerals such as selenium, molybdenum, and zinc contribute to the pathogenesis of ESCC. High levels of nitrates and nitrites, found in pickled and preserved foods, are converted to N-nitrosamines and have been associated with ESCC. Several studies have linked alcohol and tobacco use with the development of esophageal cancer, and one study found ethanol to be associated with nearly 80 percent of esophageal cancers.[1] Other predisposing conditions include long-standing achalasia, caustic injury, tylosis, and Plummer–Vinson syndrome.

### ESOPHAGEAL ADENOCARCINOMA

Barrett metaplasia, and specifically intestinal-type columnar mucosa, is the precursor lesion to EAC. Microscopically, columnar epithelium is seen with mucosal glands that contain intestinal goblet cells (Fig. 16-1A). On endoscopy, Barrett mucosa appears as red, velvety areas between smooth, pale esophageal squamous mucosa (Fig. 16-2A). After the squamous epithelium is injured chronically by reflux, there is a metaplastic change to a columnar epithelium. With further injury and multiple genetic changes, progression occurs in a metaplasia–dysplasia–adenocarcinoma sequence.

In patients with Barrett metaplasia, the risk of EAC is increased 30 to 125 times that of the age-matched

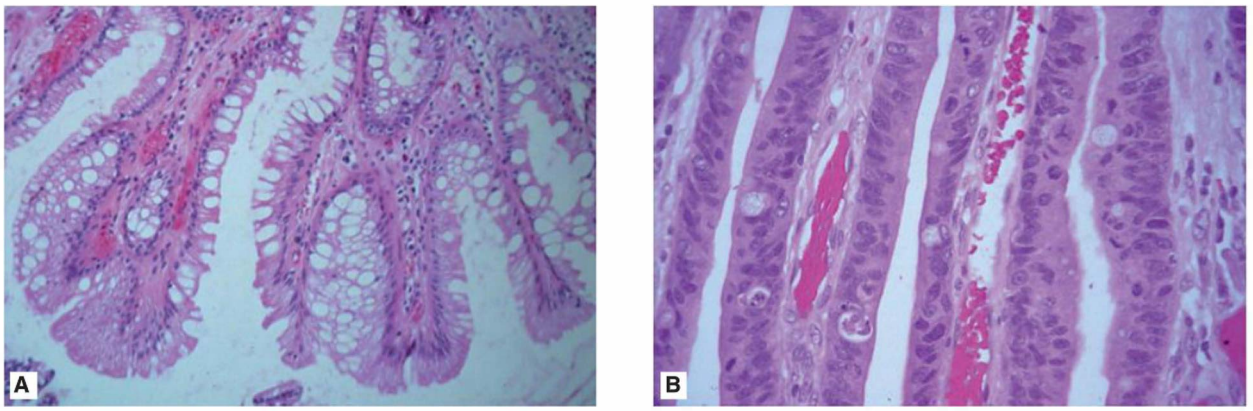



**FIGURE 16-1** Photomicrograph. **A.** Barrett mucosa showing columnar epithelium with mucosal glands containing intestinal goblet cells. **B.** High-grade dysplasia with nuclear atypia.

population. Barrett esophagus results from chronic inflammation due to gastroesophageal reflux. At endoscopy, Barrett mucosa is found in 12 to 18 percent of patients with reflux.[2] Although the esophageal mucosa is relatively resistant to acid, mixed reflux with bile acids, pepsin, and gastric acid appears to be more harmful, and up to 67 percent of patients with Barrett metaplasia have bile-stained duodenogastric reflux.

EAC is believed to have a 4- to 5-year preclinical phase, suggesting that surveillance may be effective. Cancers detected during surveillance tend to be less advanced, and the American College of Gastroenterology has suggested that patients with chronic reflux undergo upper endoscopy. Abnormal mucosa is biopsied to diagnose Barrett metaplasia and to detect the presence of dysplasia (Fig. 16-1B). Surveillance intervals are increased to every 3 years after two consecutive biopsies are negative for dysplasia.

Other risk factors for EAC include ectopic gastric mucosa, obesity, smoking, diets high in saturated fat and red meat, and medications that reduce lower esophageal sphincter pressure. Concerns have also been raised that the treatment of *Helicobacter pylori*, specifically the acid-suppressing effects of the Cag A+ strain, may actually increase the incidence of EAC.

Although the majority of ESCCs are located in the middle third of the esophagus, EACs (approximately 79 percent) arise in the distal esophagus. High-grade dysplasia (HGD) remains the best predictor of progression to adenocarcinoma. An extensive lymphatic network and the long interval during which esophageal tumors remain asymptomatic contribute to the high incidence of nodal disease with 30 to 58 percent of patients having lymph node metastases when the submucosa is involved.[3] The extent of invasion and the presence or absence of lymph node metastases are important in determining patient prognosis. The most common sites of distant metastases include the liver, lungs, bone, brain, and adrenal glands (Table 16-1).

## Clinical Features

### EPIDEMIOLOGY

In the United States, the annual incidence of ESCC is 2.6 per 100,000. The incidence is four to five times higher in African Americans than in Caucasians. Regions with a high incidence are generally located in poorer areas of the world including parts of China, Central Asia, and Latin America. The overall 5-year survival rate is approximately 15 percent.

The incidence of EAC has increased progressively from the 1970s, and esophageal adenocarcinoma is the most rapidly increasing solid malignancy in the United States. Adenocarcinoma has surpassed ESCC as the most common cancer of the esophagus in America, and esophageal carcinoma is the seventh leading cause of cancer-related deaths. The median age at diagnosis is 68. Men are affected six to eight times more frequently than are women, and Caucasians are affected three to four times as often as African Americans. The incidence is higher in developed countries.

### CLINICAL PRESENTATION

Dysphagia is the most common initial symptom but generally only occurs when the tumor involves more than 50 percent of the circumference of the esophagus. Odynophagia is the next most common symptom and may be caused by an ulcerated lesion. Constant pain in the mid-back or midchest suggests mediastinal invasion. Hoarseness may develop with proximal tumors and indicates involvement of the recurrent laryngeal nerve. Regurgitation may occur as the growing tumor narrows the esophageal lumen, and weight loss is frequently present at presentation. Although patients often have a history of reflux symptoms, clinical features do not distinguish patients with or without Barrett, which is frequently asymptomatic. The evaluation of a suspected esophageal adenocarcinoma is outlined in Figure 16-3.

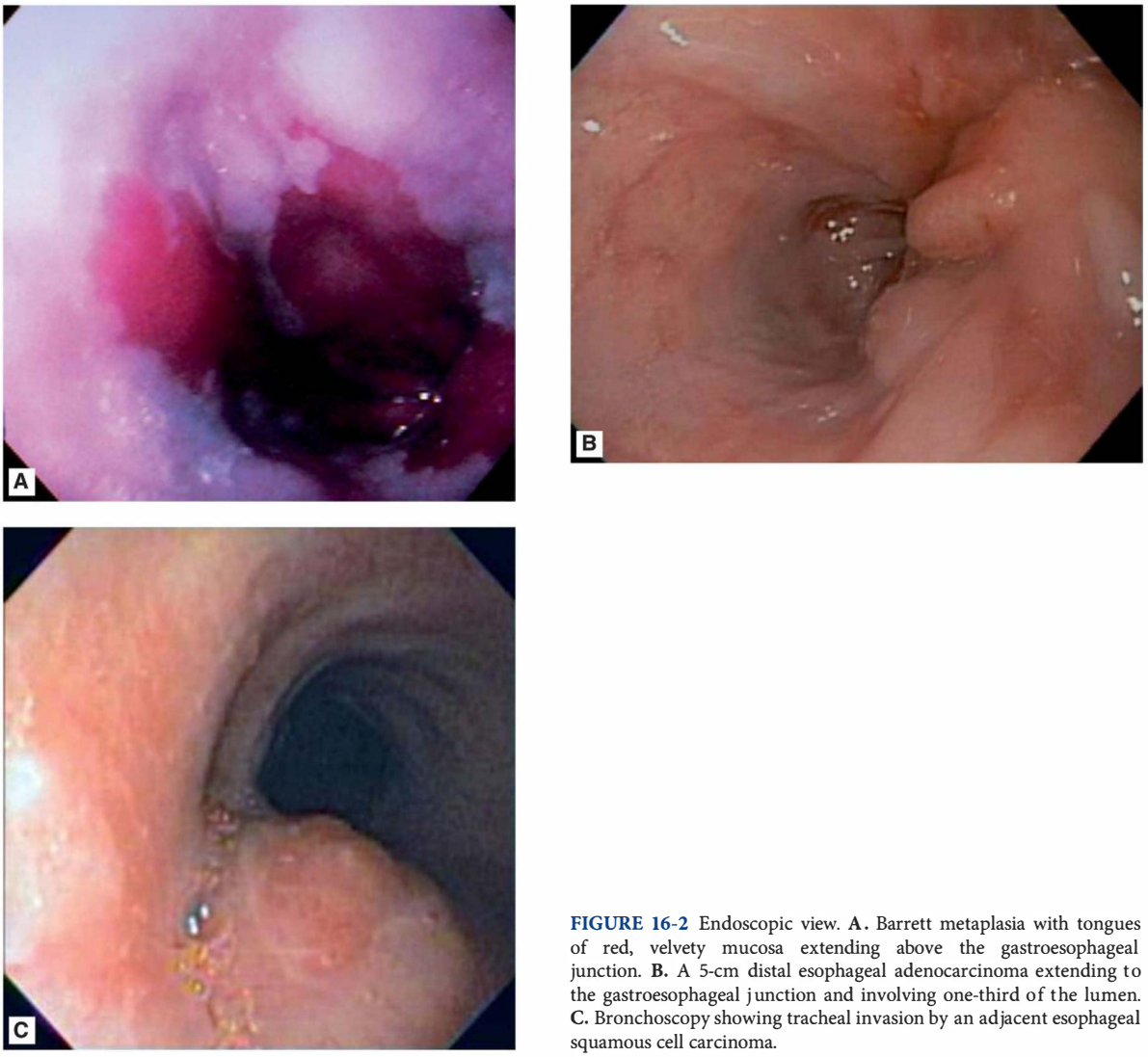



**FIGURE 16-2** Endoscopic view. **A.** Barrett metaplasia with tongues of red, velvety mucosa extending above the gastroesophageal junction. **B.** A 5-cm distal esophageal adenocarcinoma extending to the gastroesophageal junction and involving one-third of the lumen. **C.** Bronchoscopy showing tracheal invasion by an adjacent esophageal squamous cell carcinoma.

**TABLE 16-1: Occurrence of Metastases in Patients with Esophageal Cancer**

| Sites | Occurrence (%) |
|---|---|
| Liver | 35 |
| Lung | 20 |
| Bone | 9 |
| Adrenal glands | 2 |
| Brain | 2 |
| Pericardium | 1 |
| Pleura | 1 |
| Stomach | 1 |
| Pancreas | 1 |
| Spleen | 1 |

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## Diagnostic Modalities

### ENDOSCOPY

The management and prognosis of esophageal carcinoma depend on accurate clinical staging. Endoscopic evaluation is essential in all patients suspected of having esophageal carcinoma (Fig. 16-2B). The location of the lesion, degree of obstruction, and the length of the lesion should be determined in all patients. Any abnormal lesions should be biopsied. Other findings to be noted include the presence of Barrett mucosa or a hiatal hernia, and the fundus should be closely examined on retroflexion for any tumor involvement. Although advanced carcinoma is easily identified, early mucosal changes may be difficult to recognize. Chromoendoscopy with indigo carmine or acetic acid and

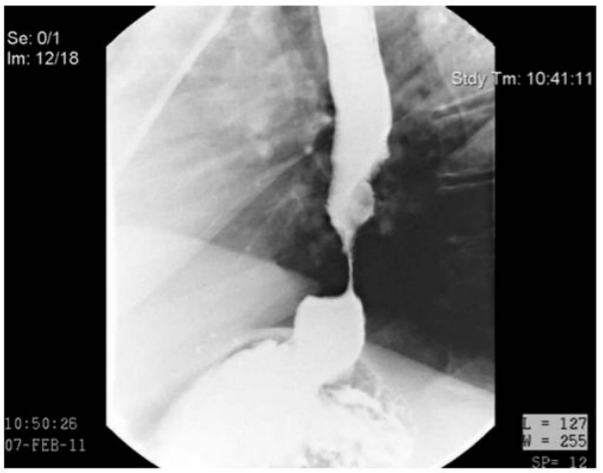



**FIGURE 16-3** Barium esophagram demonstrating a circumferential distal esophageal mass proximal to a hiatal hernia consistent with a Barrett adenocarcinoma associated with gastroesophageal reflux.

narrow band imaging can highlight mucosal details a nd the microvasculature by using blue and green light with shorter wavelengths resulting in better penetration of superficial tissues. Lugol's solution can be used to identify dysplastic squamous lesions. Normal epithelium, which contains glycogen, is stained by the iodine. New techniques are being developed to improve visualization including confocal endomicroscopy and fluorescent-labeled peptides designed to bind to dysplastic or cancerous lesions.[4] Mapping biopsies with four-quadrant biopsies obtained every 1 to 2 cm can also help to delineate abnormal lesions.

Bronchoscopy is important to evaluate possible tracheal invasion by tumors in the upper or middle thirds of the esophagus (Fig. 16-2C). Patients with infracarinal bulky tumors or subcarinal lymphadenopathy on computed tomography (CT) should also undergo bronchoscopy. Findings may range from bulging of the bronchial wall and subtle mucosal changes to frank tumor invasion or the presence of a tracheoesophageal fistula. The carina may appear widened due to subcarinal lymphadenopathy. Bronchial biopsies are obtained to confirm that airway invasion is present.

## RADIOGRAPHIC STUDIES

***Contrast Studies.*** The barium swallow is an essential diagnostic study in the evaluation of dysphagia and allows visualization of the esophageal mucosa, distensibility, and motility (Fig. 16-3). Involvement of the fundus can also be seen on the esophagram. Subtle mucosal irregularities, ulcerations, or small polypoid lesions are best seen on a double-contrast esophagram.

***Computed Tomography.*** Staging CT scans of the chest and upper abdomen are useful in the initial evaluation of esophageal carcinoma as well as assessing the response to neoadjuvant therapy. CT is used to determine the local extent of the tumor, the relationship to adjacent structures, lymphadenopathy, and the presence of distant metastases. CT cannot distinguish the layers of the esophageal wall and is not as useful in determining the T stage. However, loss of fat planes can be useful in determining invasion of adjacent structures. The sensitivity for detecting lymphadenopathy (>1 cm) is 30 to 60 percent in the mediastinum and 50 to 75 percent in the abdomen, whereas CT has a 70 to 80 percent sensitivity for identifying metastatic disease greater than 2 cm.[5]

***Endoscopic Ultrasound.*** Endoscopic ultrasound (EUS) provides the most accurate assessment of the depth of tumor invasion, or T stage, and is able to identify five distinct layers in the esophageal wall (Fig. 16-4). EUS is most useful in the staging of early carcinoma. EUS is also more sensitive in detecting regional lymphadenopathy and can evaluate the

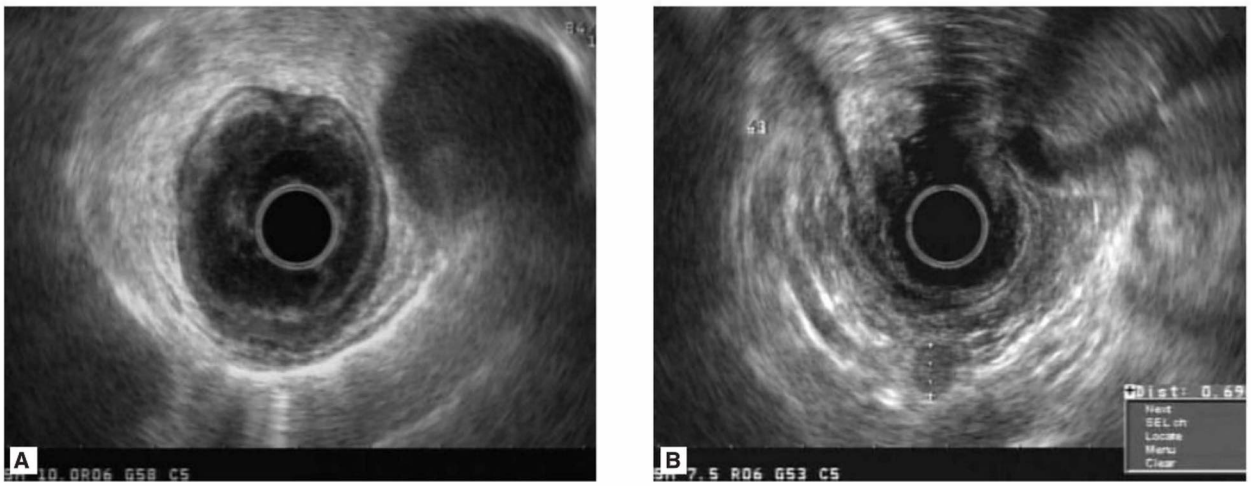



**FIGURE 16-4** **A.** Endoscopic ultrasound shows a hypoechoic 6-cm distal esophageal mass with sonographic evidence of invasion into the adventitia. **B.** Sonographic view of an abnormal hypoechoic lymph node with well-defined margins visualized in the gastrohepatic ligament.

extent of periesophageal invasion. Curvilinear arrays assist in the performance of fine-needle aspiration (FNA), which is up to 98 percent sensitive and 100 percent specific. EUS has also been evaluated for assessing the response to neoadjuvant therapy but may be prone to overstaging.

***Positron Emission Tomography.*** Positron emission tomography (PET) improves staging by identifying distant disease not seen on CT alone. PET has a higher sensitivity than CT in detecting nodal and distant metastases, although PET cannot distinguish the primary tumor from peritumoral lymph nodes. Sensitivity ranges from 78 to 95 percent, and specificity from 95 to 100 percent. The role of PET in restaging after neoadjuvant treatment needs to be further evaluated. Although studies suggest that decreased activity seen on PET corresponds with response to chemoradiation, PET is not sensitive enough to identify complete responders.

### THORACOSCOPY AND LAPAROSCOPY

Thoracoscopic and laparoscopic staging offer direct visualization and the ability to obtain biopsies to determine nodal status, the extent of local invasion, and the presence of metastatic disease and can be useful in specific circumstances. Laparoscopy should be considered in patients with suspected intraperitoneal metastases to assess for tumor implants whereas thoracoscopy is useful to evaluate for small pulmonary nodules or mediastinal lymph nodes not accessible by endobronchial ultrasound (EBUS) or CT-guided biopsy. Laparoscopic ultrasound is also being investigated as a staging modality and may provide improved accuracy in T and N staging. Laparoscopic ultrasound may be more accurate in staging celiac nodes than EUS, providing closer access for the ultrasound probe as well as direct inspection.

### STAGING

Accurate staging is essential for treatment selection, and the stage at diagnosis is the most important prognostic factor. The evaluation of patients with suspected esophageal cancer should include appropriate diagnostic studies as described above as well as biopsies of any suspected metastatic lesions (Fig. 16-5). Although patients with stage I tumors have a 65 percent 5-year survival, those with biopsy-proven distant metastatic disease have a mean survival of only 6 months and are considered unresectable. Both esophageal squamous cell and adenocarcinoma are staged according to the American Joint Committee for Cancer TNM system. Significant changes in the 7th edition take into account the histology, grade, and number of regional lymph nodes involved.

## Medical Therapy

### RADIATION THERAPY

Results of a large review published by Earlam and Cunha-Melo with more than 8000 inoperable patients due to prohibitive surgical risk or unresectable esophageal carcinoma showed 1-, 2-, and 5-year survival rates of 18, 8, and 6 percent after definitive radiotherapy.[6] Postoperative radiotherapy has been shown to decrease local recurrence but has not improved survival rates. Several trials of neoadjuvant radiotherapy have also failed to show increased resection rates or improved survival compared with surgery alone.

### CHEMOTHERAPY

Law et al. showed that neoadjuvant chemotherapy resulted in significant downstaging of disease in nearly 50 percent of patients, but a pathologic complete response was seen in less than 10 percent.[7] A marginal survival benefit was noted in this subgroup of patients. Kelsen et al. reported a large multicenter study of neoadjuvant chemotherapy versus surgery alone, which included 440 patients. At 2-year follow-up, no significant survival benefit was seen.[8]

### CHEMORADIOTHERAPY

The Radiation Therapy Oncology Group (RTOG) randomized trial reported by Al-Sarraf et al. provided convincing evidence of the superiority of chemoradiation over radiation alone.[9] The 2- and 5-year survival rates were 36 and 27 percent in the chemoradiation group compared with 10 and 0 percent in the group treated with radiation alone. There was also a reduction in both local recurrence and distant disease. However, the toxicity of the treatments was significant. Many surgeons advocate neoadjuvant therapy for patients with esophageal carcinoma, except in patients with early disease, due to the poor survival rates following resection alone. Neoadjuvant chemoradiotherapy is routine at the University of Michigan in patients with tumors staged as T2 or greater or patients with positive nodal disease (Fig. 16-5). Neoadjuvant therapy is limited to patients younger than 75 years due to the significant toxicity and the decrease in patients able to complete trimodality therapy with increasing age.

The combination of chemoradiation with surgery has resulted in significant downstaging of disease, but a survival advantage has not been consistently demonstrated in randomized trials. Most regimens are cisplatin-based and commonly combined with 5-fluorouracil. Chemoradiation is followed by resection 5 to 6 weeks after completion of therapy. Walsh et al. reported a randomized trial of 113 patients receiving neoadjuvant therapy or surgery alone and showed significantly improved survival after neoadjuvant treatment of 17 months versus 12 months.[10] However, the survival in the surgery arm was lower than most published series. Urba et al. performed a randomized trial of 100 patients who underwent either transhiatal esophagectomy following neoadjuvant chemoradiation therapy or surgery alone.[11] Seventy-five percent of patients had adenocarcinoma. Twenty-eight percent had a complete pathologic response. Survival at 3 years was 30 percent after neoadjuvant therapy versus 16 percent after surgery alone although this was not statistically significant.

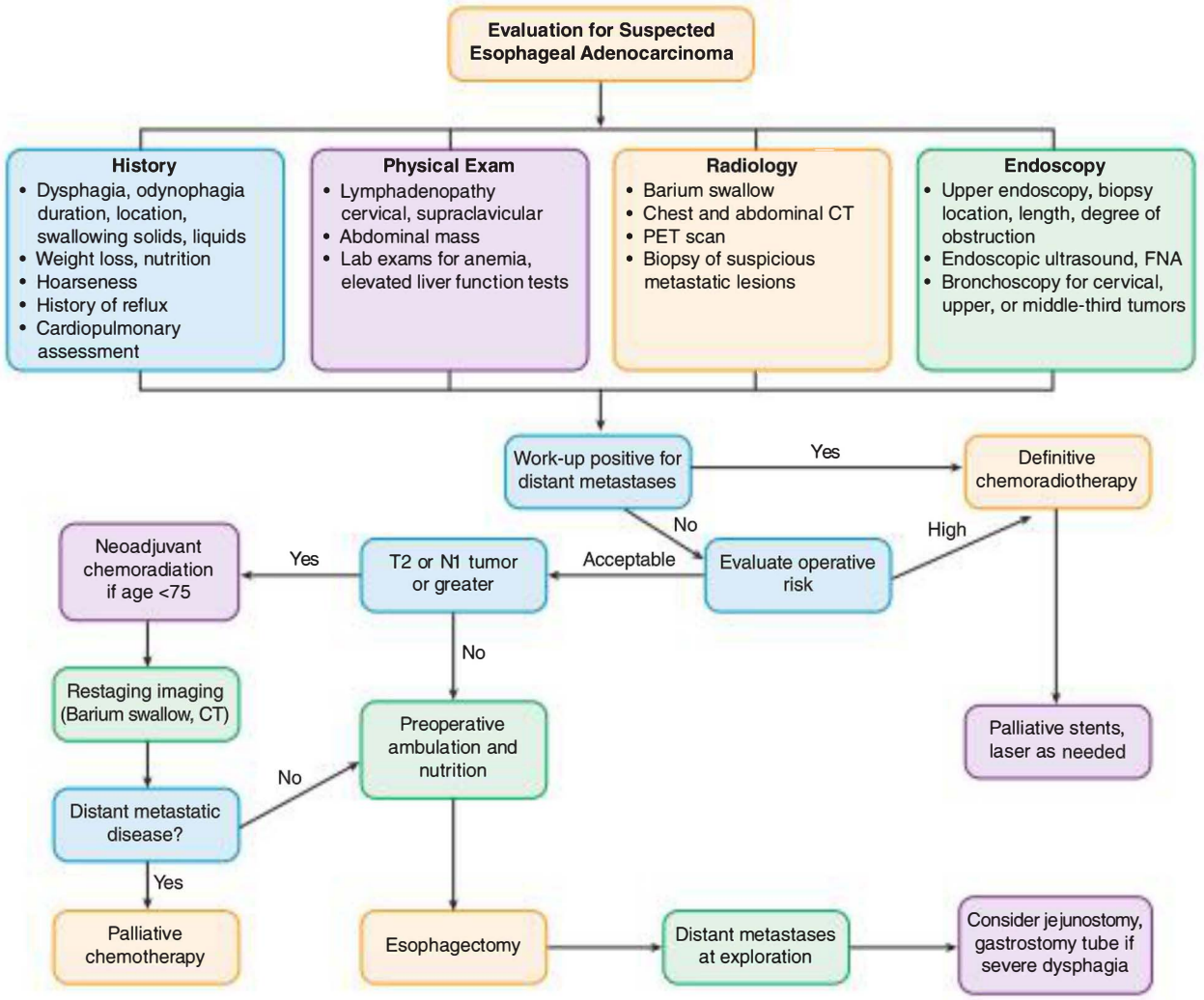



**FIGURE 16-5** Diagnostic algorithm in the evaluation of a patient with suspected esophageal adenocarcinoma. FNA, fine-needle aspiration.

A meta-analysis of randomized trials comparing trimodality therapy with surgery alone showed a slight increase in overall survival with a complete pathologic response associated with the best survival.[12] Gebski et al. performed a meta-analysis including 1200 patients undergoing neoadjuvant chemoradiation and found a hazard ratio (HR) of 0.81 (95 percent CI 0.70–0.93; $p = 0.002$).[13]

Cancer and Leukemia Group B (CALGB) 9781 was a prospective, randomized phase III trial comparing trimodality therapy with cisplatin and 5-FU to surgery alone.[14] Although the study was closed early due to low accrual after 56 patients, the authors reported a 5-year survival of 39 percent compared with 16 percent in patients undergoing surgery alone supporting the use of trimodality therapy. Newer agents including taxanes and irinotecan are being evaluated in chemoradiotherapy trials and may have promising antitumor activity as well as improved tolerance.

## TARGETED THERAPIES

In addition, new targeted therapies against growth factor receptors such as EGFR and HER-2/Neu and angiogenesis factors including VEGF are being investigated in the treatment of esophageal carcinoma. Inhibitors include small-molecule tyrosine kinase inhibitors and monoclonal antibodies. Several phase II trials evaluating EGFR inhibitors have been completed in patients with advanced esophageal carcinoma with modest response rates seen in 10 percent of patients.[15] Larger phase III trials will be needed to determine which patients may benefit from therapy. The ToGA trial was a randomized, prospective phase III trial evaluating 594 patients with advanced HER-2-positive gastric and gastroesophageal junction (17–20 percent of patients) tumors with cisplatin and 5-FU with or without trastuzumab, an anti-HER-2 monoclonal antibody.[16] There was a significant increase in survival of 13.5 versus

11.1 months (HR 0.74; 95 percent CI 0.60–0.91; $p = 0.046$) and progression-free survival of 6.7 versus 5.5 months. Complete response was seen in 5 percent versus 2 percent and a partial response in 42 percent versus 32 percent. Patients with high HER-2 expression had a median overall survival of 16 months (HR 0.65; 95 percent CI 0.51–0.83). For the subgroup of patients with gastroesophageal junction tumors, The HR was 0.67 (95 percent CI 0.42–1.08). Trastuzumab was recently added to the National Comprehensive Cancer Network Guidelines for combination treatment of advanced esophageal and gastric adenocarcinomas. RTOG 1010 is currently accruing patients in a phase III trial evaluating the addition of trastuzumab to trimodality therapy in HER-2 overexpressing esophageal adenocarcinomas.

At this time, surgery remains the standard treatment for resectable esophageal carcinoma. For patients with advanced disease or those unfit for surgery, chemoradiation therapy appears to be a reasonable alternative.

## ENDOSCOPIC THERAPIES

***Mucosal Ablation.*** Some investigators have had success with mucosal ablation of Barrett mucosa with squamous re-epithelialization. Effective antireflux therapy is critical. Techniques include laser, photodynamic therapy, cryotherapy, and radiofrequency ablation. Salo et al. reported successful Nd-YAG laser ablation after antireflux surgery in 11 patients who had complete squamous regeneration after a mean of 26 months.[17] However, Wang and Sampliner have found persistent areas of intestinal metaplasia underlying the squamous epithelium.[18]

Photodynamic therapy (PDT) involves the systemic injection of a photosensitizer, porfimer sodium, targeting dysplastic cells. After 24 to 48 hours, light is used to produce oxygen radicals. All devitalized tissue is irrigated away 48 hours later. Using this technique, Overholt et al. reported 90 percent of lesions cleared or downstaged to low-grade dysplasia although 83 percent required repeat laser treatment 3 to 6 months later for residual Barrett mucosa.[19] Esophageal mucosal re-epithelialization occurred over 2 to 3 months and was complicated by strictures in 34 percent. Patients also need to avoid sun exposure due to photosensitivity for up to 3 months.

In the prospective, multicenter AIM-II trial endoscopic radiofrequency ablation was evaluated in patients with nondysplastic Barrett mucosa. Complete eradication was achieved in 98.4 percent of patients at 2.5 years and 92 percent at 5 years (46/50 patients). The four patients with focal Barrett were re-treated with RFA. The authors reported no buried glands, dysplasia, or strictures. Although this technique may be useful for Barrett mucosa, as an ablative procedure, pathology specimens are not obtained, and ablation should not be used for HGD or esophageal carcinoma where pathologic examination to determine the histology, depth of invasion, lymphovascular involvement, and margins is critical.

***Endoscopic Mucosal Resection.*** Endoscopic mucosal resection (EMR) was first reported in Japan and involves injecting saline and epinephrine into the submucosal space to elevate the target area, which is then lifted with a suction cap or banded and removed with a polypectomy snare. Failure of the lesion to lift after saline injection suggests submucosal invasion. High-frequency EUS is useful in defining the depth of invasion prior to resection. Risks include bleeding, perforation, and stricture. The overall complication rate is 13 to 17 percent.[20] Strictures are reported in 6 to 23 percent of cases and are more likely after circumferential EMR or in combination with ablation such as PDT. The risk of bleeding is 0.6 to 11 percent. Bleeding requiring transfusions occurs in 3.8 percent, and perforation occurs in 0 to 2.5 percent.

Recurrence of dysplasia or carcinoma has been reported in 12 to 21 percent of patients with a mean follow-up of 43 to 63 months although these lesions were often treated with repeat EMR.[20] The risk of recurrence is increased with long-segment Barrett (relative risk 1.9; 95 percent CI 1.06–3.3), larger lesions requiring piecemeal resection (RR 2.44; 95 percent CI 1.13–4.89), and multifocal carcinoma (RR 2.1; 95 percent CI 1.16–3.99). Residual metaplastic mucosa can also persist beneath the regenerating squamous mucosa. Close endoscopic follow-up is mandatory and persistent lesions, involvement of the submucosa, or positive margins warrants an esophagectomy.

HGD is being treated increasingly with EMR although esophagectomy remains the gold standard. Another alternative is intensive surveillance with four-quadrant biopsies taken every centimeter and repeated every 3 months. However, there are inherent false negatives as biopsies may miss dysplasia and carcinomas separated by large areas of Barrett epithelium. Several retrospective studies have shown difficulty in differentiating HGD from adenocarcinoma using endoscopic surveillance. In addition, the majority of patients with HGD will have invasive adenocarcinoma develop within 10 years with 25 percent at 1.5 years, 50 percent at 3 years, and 80 percent at 8 years on surveillance biopsies. Zhu et al. evaluated 127 esophagectomy specimens performed for high-grade dysplasia.[21] Patients with biopsies showing only HGD were found to have adenocarcinoma in 5 percent of esophagectomy specimens while more than 80 percent of patients with HGD suspicious for carcinoma were found at resection to have adenocarcinoma suggesting that these patients may be more appropriately treated as patients with carcinoma.

Early intramucosal carcinomas (T1a) have also been treated with endoscopic resection especially in debilitated patients who are not surgical candidates. EACs confined to the mucosa have 1 to 5 percent risk of lymph node metastases while invasion of the submucosa increases the risk to 30 to 58 percent.[3,20] Long-term results are not yet available and surgery remains the gold standard with curative intent in these patients.

***Surgical Therapy.*** Surgical therapy currently offers the best chance for cure with a complete R0 resection and provides

effective palliation with relief of dysphagia. Although mortality rates have decreased significantly over the past few decades, relatively high postoperative morbidity remains. Appropriate pulmonary and cardiac evaluation as well as aggressive preoperative preparation including preoperative ambulation, nutrition, incentive spirometry, patient education, and smoking cessation are critical. Although the goal is to proceed with resection 5 to 6 weeks after completion of neoadjuvant therapy, it is important to wait until patients have returned to their baseline function prior to proceeding with esophagectomy.

Controversy continues to surround the optimal surgical approach to esophagectomy as well as the extent and necessity of regional lymph node dissection. Proponents of the combined thoracotomy and laparotomy approach described by Ivor Lewis emphasize the direct visualization during mediastinal dissection, an en bloc resection, and a wider lymphadenectomy resulting in improved staging. Two meta-analyses comparing the two approaches showed higher perioperative morbidity and mortality after the transthoracic approach with no difference in long-term survival.[22,23] The choice of approach depends on the location of the tumor, planned extent of lymphadenectomy, and the preference of the surgeon. The role of palliative resection is limited with the availability of esophageal stents, laser ablation, and radiation therapy.

***Transhiatal Esophagectomy.*** The transhiatal approach avoids the morbidity of a thoracotomy in debilitated patients as well as the potential occurrence of a disastrous intrathoracic anastomotic disruption. Although accessible subcarinal, paraesophageal, and celiac lymph nodes are sampled, no attempt is made to perform an en bloc resection. Although critics have questioned the oncologic principles arguing for the need to perform an aggressive mediastinal lymph node resection, survival has been reported in several series to be equivalent to that seen after a transthoracic resection. Transhiatal esophagectomy is technically possible in the majority of patients even with a history of prior operations, esophageal perforation, or radiation treatment and provides a maximal esophageal margin. In addition, the stapled side-to-side cervical anastomosis has decreased the anastomotic leak rate to less than nine percent at the University of Michigan, and most cervical leaks are treated conservatively by opening the wound at the bedside and dressing changes.[24,25] Less frequent complications include intrathoracic hemorrhage, recurrent nerve paralysis, and tracheal laceration.

## OPERATIVE TECHNIQUE

***Abdominal Phase.*** The abdomen is entered through a midline supraumbilical incision, and the liver and peritoneal cavity are examined for metastatic disease. The triangular ligament is divided, and the stomach is carefully examined for tumor involvement. The right gastroepiploic artery is identified and protected. This may be difficult if there is a history of previous abdominal surgery. The left gastroepiploic and short gastric vessels are ligated, and the esophagogastric junction is mobilized. After examining the gastrohepatic ligament for a replaced left hepatic artery, the left gastric artery is ligated near its origin taking the left gastric lymph nodes with the specimen. The right gastric artery is preserved as the dissection is continued along the lesser curvature. A Kocher maneuver is then performed to allow mobilization of the pylorus to the level of the hiatus. A pyloromyotomy is performed to decrease the incidence of postvagotomy delayed gastric emptying. Clips are placed at the level of the pyloromyotomy for future radiographic studies. A jejunostomy tube is placed and is used as needed to supplement postoperative nutrition.

The distal 5 to 10 cm of esophagus is mobilized through the hiatus. The mobility of the esophageal tumor is then assessed to ensure that there is no invasion of the prevertebral fascia, aorta, or surrounding mediastinal structures. Deaver retractors inserted into the hiatus allow ligation of the periesophageal tissues to the level of the carina under direct vision using long right-angle clamps.

***Cervical Phase.*** An oblique incision is made along the anterior border of the sternocleidomastoid muscle. Care is taken to avoid retraction on the left recurrent laryngeal nerve in the tracheoesophageal groove. The middle thyroid vein and inferior thyroid artery are ligated as needed. After dissecting down to the prevertebral fascia, blunt finger dissection is continued into the superior mediastinum. Sharp dissection is used along the anterolateral surface of the esophagus staying posterior to the recurrent laryngeal nerve. The upper thoracic esophagus is mobilized almost to the level of the carina using blunt dissection keeping the fingers directly on the esophagus.

***Mediastinal Dissection.*** One hand is inserted through the diaphragmatic hiatus posterior to the esophagus while a sponge stick is placed through the cervical incision dissecting the esophagus off the prevertebral fascia (Fig. 16-6A). The blood pressure is carefully monitored to prevent hypotension, and a sump catheter is inserted through the cervical incision to evacuate blood from the posterior mediastinum. The anterior mobilization is performed from both the abdominal and the cervical incisions with the fingers directly against the anterior esophagus to avoid injury to the membranous trachea. The esophagus is held in the superior mediastinum between the index and middle fingers of the hand inserted through the hiatus, and the remaining attachments are lysed with a downward motion (Fig. 16-6B). A partial upper sternotomy can be performed for improved exposure in patients with a short, broad neck or poor neck extension. The upper esophagus is then divided obliquely, and the thoracic esophagus is delivered through the diaphragmatic hiatus. Using Deaver retractors, the posterior mediastinum is inspected for hemostasis through the hiatus. If the pleural cavities have been entered, which occurs in three-quarters of cases, chest tubes are placed. The posterior mediastinum is temporarily packed with gauze pads to tamponade minor bleeding.

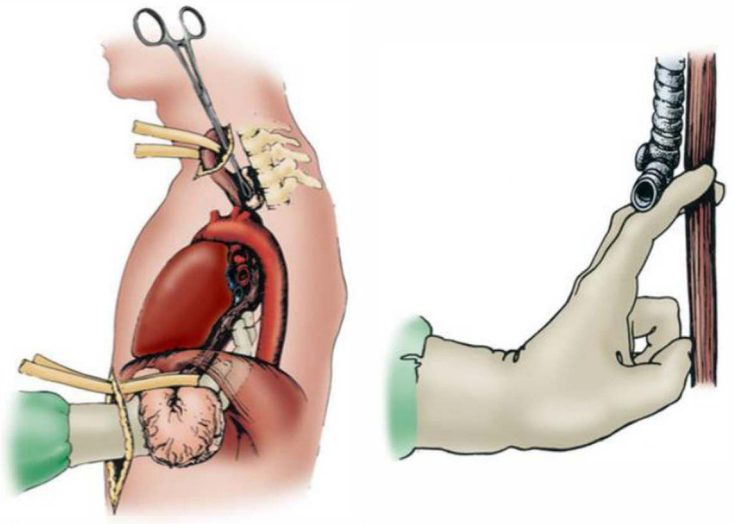



**FIGURE 16-6** **A.** Esophageal mobilization from the prevertebral fascia is performed using a half-sponge stick from the cervical wound and a hand inserted through the diaphragmatic hiatus. (From Orringer MB, Sloan H. Esophagectomy without thoracotomy. *J Thorac Cardiovasc Surg* 1978;76(5):643–654. Copyright Elsevier.) **B.** A downward raking motion with the esophagus held between the index and the middle fingers is used to take down the lateral periesophageal attachments. (From Orringer MB. Transhiatal blunt esophagectomy without thoracotomy. In: Cohn LH (ed.). *Modern Techniques in Surgery*, Vol. 62. Cardiovascular Surgery. New York: Futura Publishing, 1983:1.)

A partial proximal gastrectomy 4 to 6 cm distal to the esophagogastric junction is performed using a GIA stapler (Fig. 16-7A). For tumors of the middle esophagus or benign disease, the amount of stomach resected is minimized to preserve collateral circulation to the fundus. The staple line is oversewn. The mobilized stomach is passed through the hiatus and delivered 4 to 5 cm above the clavicles by pushing the stomach up through the mediastinum and guiding it with a Babcock clamp from the cervical incision (Fig. 16-7B). Traction sutures and suction devices to pull the stomach

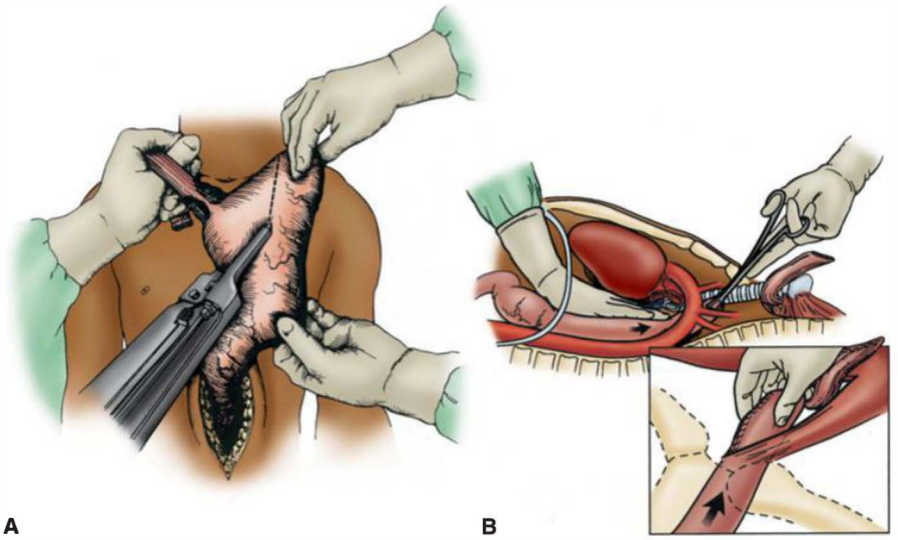



**FIGURE 16-7** **A.** Partial proximal gastrectomy is performed by sequentially applying the GIA stapler. (Reproduced with permission from Orringer MB, Sloan H. Esophageal replacement after transhiatal esophagectomy without thoracotomy. In Nyhus LM, Baker RJ (eds). *Mastery of Surgery*, 2nd ed. Boston: Little, Brown, 1992:569.) **B.** The mobilized stomach is gently passed into the posterior mediastinum. A Babcock clamp is used to carefully grasp the stomach in the superior mediastinum, but the stomach is delivered primarily by pushing from below. (Reproduced with permission from Orringer MB, Marshall B, Iannettoni MD. Eliminating the cervical esophagogastric anastomotic leak with a side-to-side stapled anastomosis. *J Thorac Cardiovasc Surg* 2000;119(2):277–288. Copyright Elsevier.)

through the mediastinum are avoided to minimize trauma to the gastric conduit. Care is taken to ensure that there is no torsion of the conduit.

The abdominal phase is then completed to avoid contamination with bacteria from the cervical esophagus. The diaphragm is reapproximated using silk sutures so that the hiatus allows three fingers to pass alongside the stomach. The anterior gastric wall is approximated to the edge of the hiatus, and the triangular ligament is re-attached to the diaphragm to help prevent a hiatal hernia. The pyloromyotomy is covered with omentum.

***Cervical Esophagogastric Anastomosis.*** A traction suture is placed in the anterior gastric wall to elevate the stomach into the wound. A 1.5-cm vertical gastrotomy is made in the anterior gastric wall low enough down to allow the Endo GIA to be fully inserted into the stomach (Fig. 16-8A). The cervical esophageal staple line is then amputated obliquely with enough redundancy for a tension-free anastomosis and sent to pathology as the proximal esophageal margin. After placing stay sutures to align the stomach and esophagus, the Endo GIA is inserted and closed (Fig. 16-8B). Before opening the stapler, two suspension sutures between the esophagus and adjacent stomach are placed on either side of the anastomosis. After removing the stapler, a nasogastric tube is guided across the anastomosis, and the anterior wall of the anastomosis is reapproximated in two layers (Fig. 16-8C). Clips are placed beside the anastomosis as radiographic markers, and the wound is closed after placing a penrose drain.

***Minimally Invasive Approaches.*** Luketich et al. reported a series of 222 patients undergoing a minimally invasive laparoscopic and thoracoscopic approach with a cervical anastomosis.[26] A pyloroplasty is performed and the cervical anastomosis is completed using an EEA stapler. Neoadjuvant chemotherapy was used in 35.1 percent and radiation in 16.2 percent. Conversion to an open esophagectomy was performed in 7.2 percent. The average hospital stay was 7 days, and operative mortality was 1.4 percent. The anastomotic leak rate was 11.7 percent. The leak rate was affected by the width of the gastric conduit with a leak rate of 6.1 percent with a conduit greater than 6 cm in width versus 25.9 percent with a narrower conduit. Recurrent laryngeal nerve injury occurred in 3.6 percent and pneumonia in 7.7 percent.

More recently, this group has described performing a minimally invasive Ivor Lewis esophagectomy in 50 patients.[27] Fifteen of the patients were approached by thoracoscopy while the remainder had a planned mini thoracotomy for the anastomosis that was performed with an EEA stapler. The operative mortality was 6 percent and the leak rate 6 percent. Although there were no recurrent laryngeal nerve injuries with avoidance of the cervical dissection, a return to an intrathoracic anastomosis could increase the morbidity of an intrathoracic leak compared with the relatively benign consequences of a cervical anastomotic leak.

Minimally invasive esophagectomy is technically demanding and should be performed in centers with extensive laparoscopic and thoracoscopic experience. Care must be taken to balance the benefits of smaller incisions and less pain

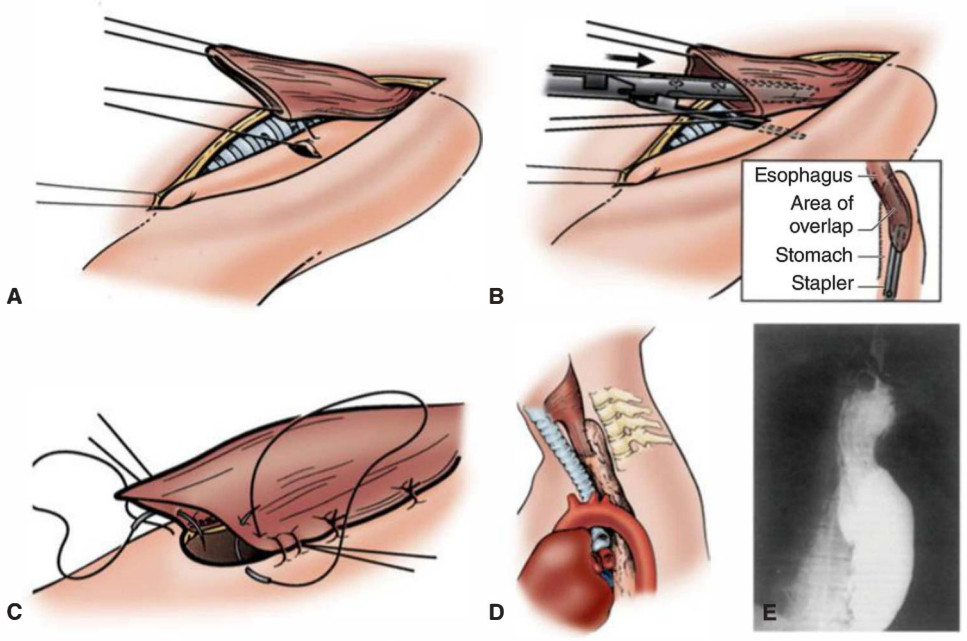



**FIGURE 16-8** Cervical stapled side-to-side anastomosis after transhiatal esophagectomy. **A.** The esophagogastrostomy is aligned using stay sutures. **B.** An Endo-GIA stapler is inserted. **C.** The semimechanical anastomosis is completed. **D.** The completed cervical side-to-side anastomosis. **E.** Postoperative barium swallow. (Reproduced with permission from Orringer MB, Marshall B, Iannettoni MD. Eliminating the cervical esophagogastric anastomotic leak with a side-to-side stapled anastomosis. *J Thorac Cardiovasc Surg* 2000;119(2):277–288. Copyright Elsevier.)

from retraction with not compromising key components of the esophagectomy including avoiding trauma to the gastric conduit, adequately unrolling the stomach so that it reaches to the neck without tension, making an adequate mediastinal tunnel to avoid venous congestion of the conduit, and performing an adequate gastric drainage procedure. Further prospective studies are needed to determine if there are significant differences in costs, complication rates, and postoperative pain and recovery.

***Outcomes/Prognosis.*** Five-year survival for patients with esophageal carcinoma remains poor at less than 15 percent. Tumor stage and lymph node status are the strongest predictor of survival. Other factors associated with a poor prognosis include increased age, African American race, lower esophageal tumors, and increasing length and depth of the tumor. Five-year survival greater than 80 percent can be seen after esophagectomy for early lesions limited to the mucosa, and early diagnosis continues to be the best strategy for improving survival. Overall, esophagectomy is potentially curative in 20 percent of patients.

Orringer et al. reported the largest experience with transhiatal esophagectomy in 2007 patients.[24] When comparing group I (1976–1998) and group II (1998–2006), there was a significant decreases in in-hospital mortality (4 vs. 1 percent). A gastric conduit was used in 97 percent of patients and only 4 percent of patients in group II required intensive care postoperatively. Complications included recurrent nerve palsy (<1 percent), atrial fibrillation (6.6 percent), and pneumonia (2 percent). The incidence of anastomotic leak decreased from 14 to 9 percent in group II ($p$ <0.001) and correlated with the introduction of the side-to-side cervical esophagogastric anastomosis in 1997.[25] Ninety-four percent of those with leaks were treated with wound packing alone. Chylothorax occurred in less than 1 percent and should be treated aggressively with thoracic duct ligation. Fifty percent of patients in group II were discharged at 1 week with a median length of stay of 8 days. In cancer patients, functional results were good in 80 and 75 percent reporting no regurgitation or dumping. Fifty-two percent of patients in group II underwent neoadjuvant chemoradiation. A complete pathologic response was found in 21 percent of patients with a significant improvement in 5-year survival of 58 percent in complete responders compared with 22 percent for those with residual disease.

***Hospital Volume.*** Several studies have evaluated the relationship of hospital volume to outcomes after a variety of complex procedures including coronary artery bypass grafting, aortic aneurysm repair, heart transplantation, and pancreatic resections. Esophagectomy is technically demanding, and outcomes have been shown to be related to hospital volume. Dimick et al. reviewed 1136 patients in a Maryland statewide database and found that high-volume centers, defined as hospitals performing greater than 15 esophagectomies per year, had a fivefold reduction in hospital mortality.[28] Kuo et al. found similar results in 1193 patients in Massachusetts with a 2-day decrease in length of stay and a 3.7-fold decrease in hospital mortality in centers performing greater than six esophagectomies per year.[29] Outcomes have also been associated with the experience of the individual surgeon. Miller et al. found a significant decrease in hospital mortality rates in patients treated by surgeons who perform greater than six esophagectomies per year.[30]

## CONCLUSIONS

The evaluation and management of esophageal cancer continues to present a significant challenge for the thoracic surgeon. The incidence of EAC has increased rapidly and is the fastest growing solid malignancy in the United States. Although advances have been made in surgical techniques and postoperative care resulting in significantly improved perioperative mortality rates, the overall prognosis for patients with esophageal carcinoma remains poor and highlights the need for novel diagnostic, staging, and treatment modalities.

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## ESOPHAGEAL CANCER BOARD REVIEW QUESTIONS (CHAPTER 16)

1. Which of the following risk factors is LEAST associated with the development of esophageal squamous cell carcinoma?

   A. Molybdenum deficiency
   B. Diet high in N-nitrosamines
   C. Achalasia
   D. Alcohol use
   E. Obesity

2. The best diagnostic study for evaluating the extent of tumor invasion (T stage) is?

   A. PET scan
   B. CT scan
   C. Endoscopic ultrasound
   D. Barium swallow
   E. Bronchoscopy

3. Which of the following is true regarding the use of neoadjuvant chemoradiation?

   A. The majority of randomized studies have not found a significant difference in survival.
   B. Neoadjuvant treatment is used to downstage tumors in patients with invasion of surrounding structures such as the aorta.
   C. Patients with T1 tumors are most likely to achieve a complete response.
   D. Complete response is a good prognostic factor and is seen in 64 percent of patients.
   E. Surgery should be performed within 2 weeks of neoadjuvant therapy to minimize postradiation adhesions.

4. Which of the following is true regarding Barrett mucosa?

   A. Barrett mucosa is a precursor to esophageal adenocarcinoma and is congenital in origin.
   B. Esophageal adenocarcinoma can develop within short segment Barrett mucosa.
   C. Barrett mucosa is a risk factor for esophageal squamous cell carcinoma.
   D. Patients with Barrett mucosa require close follow-up every 3 months.
   E. Barrett mucosa develops in 40 percent of patients with long-standing reflux.

5. Which of the following is true regarding a transhiatal esophagectomy?

   A. A narrow gastric conduit is preferable.
   B. Esophagectomy is potentially curative in 20 percent of patients.
   C. The gastric conduit is based on the left gastroepiploic artery.
   D. Esophagectomy is contraindicated in patients with carcinoma that has metastasized to one periesophageal lymph node.
   E. Neoadjuvant radiation alone is indicated in patients with T3 tumors or greater.

## ANSWERS

1. **Answer: E.** Nutritional deficiencies, including low levels of vitamins A, C, and riboflavin as well as mineral elements such as selenium, zinc, and molybdenum, have been found to contribute to the pathogenesis of esophageal squamous cell carcinoma (ESCC). High levels of N-nitrosamines in pickled vegetables and preserved meats have also been associated with ESCC, and several studies have linked alcohol and tobacco use with the development of ESCC. Other predisposing conditions include long-standing achalasia, caustic injury, tylosis, and Plummer–Vinson syndrome. Obesity has been associated with the development of esophageal adenocarcinoma.

2. **Answer: C.** CT can determine the local extent of disease when there is bulging or thickening of the airway or involvement of the aorta. However, CT, PET, and barium swallow cannot distinguish the layers of the esophageal wall. EUS provides the most accurate assessment of the depth of tumor invasion, or T stage, and is able to identify five distinct layers in the esophageal wall. Bronchoscopy is useful in evaluation for airway involvement by tumors in the upper or middle thirds of the esophagus.
3. **Answer: A.** Tumors directly invading the aorta are not resectable, and neoadjuvant therapy is not indicated in patients with T1 tumors who can proceed directly to resection. A complete response is a good prognostic sign and occurs in approximately 20 percent of patients with a significant improvement in survival. Surgery should be performed approximately 5 to 6 weeks after chemoradiation, although it is important to wait until the patients have returned to their baseline function prior to proceeding to esophagectomy. This provides sufficient time for edema to resolve, for restaging imaging to be performed, and prior to the onset of radiation fibrosis. Although most randomized trials have not shown a significant improvement in survival, two meta-analyses have shown a slight increase in overall survival with a hazard ratio (HR) of 0.81.
4. **Answer: B.** Barrett mucosa is a premalignant lesion that increases one's risk of developing esophageal adenocarcinoma (EAC) by 30- to 125-fold. Approximately 12 to 18 percent of patients with gastroesophageal reflux will have Barrett mucosa on endoscopy. Barrett can be continuous or discontinuous, and cancer can develop in short-segment Barrett. Endoscopic follow-up is important for the early detection of carcinoma and can be performed every 3 years as long as no dysplasia is found on two consecutive endoscopies.
5. **Answer: B.** Patients with distant metastatic disease are not candidates for esophagectomy. However, patients with regional nodal disease should undergo resection after neoadjuvant treatment with the removal of any clinically positive lymph nodes. Overall, esophagectomy is potentially curative in 20 percent of patients. Patients with early-stage disease or complete response after neoadjuvant therapy have the best prognosis. The gastric conduit is based on the right gastroepiploic artery and should be greater than 6 cm in width to preserve collateral circulation.

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# 17 Mediastinal Disease

*Lee Plantmason*
*Natalie Lui*
*Pierre Theodore*

## KEY CONCEPTS

- Epidemiology
  - Thymic tumors are the most common primary neoplasm of the anterior mediastinum, accounting for about 20 percent of anterior mediastinal masses. Their peak incidence is in middle-aged adults between the ages of 30 and 50 years. Although lymphomas are the most common neoplasm of the mediastinum, primary mediastinal lymphomas are rare and account for less than 10 percent of lymphomas. Mediastinal germ cell tumors, including both seminomas and nonseminomas, account for about 20 percent of anterior mediastinal masses and, with the exception of teratomas, occur almost exclusively in males. All of these tumors have a peak incidence in young adults in their third decade of life. In general, extragonadal germ cell tumors are rarely primary tumors, with the mediastinum frequently being a site of metastasis.
- Pathophysiology
  - Pathophysiologic processes range from the antibody-mediated effects of myasthenia gravis (MG) seen with thymoma to the mass effects of tumors as noted in superior vena cava (SVC) syndrome. The primary mediastinal lymphomas include Hodgkin, non-Hodgkin, and lymphoblastic lymphomas. Seminomas, which occur exclusively in men, are generally malignant but highly responsive to treatment, whereas nonseminomas can range from benign teratomas that have a very low percentage of malignant transformation (<1 percent) to primary mediastinal nonseminomatous germ cell tumors that have a very poor prognosis.
- Clinical features
  - The majority of patients with thymoma are asymptomatic at presentation with an incidentally discovered mass on imaging. Those who do present symptomatically have symptoms associated with local compression or invasion, such as chest pain, cough, or dyspnea. About one-half of patients with thymoma have MG and present with muscle weakness, diplopia, ptosis, or blurry vision. Lymphomas commonly present with "B-type" symptoms of fever, night sweats, weight loss, and malaise, in addition to mediastinal compression symptoms. Most patients with seminomas and nonteratomal nonseminomas present with systemic endocrine changes such as gynecomastia. In contrast, most patients with teratomas will have compression of nearby structures causing cough and dyspnea, or direct connection with the bronchial tree causing expectoration of teratoma contents.
- Diagnostics
  - The primary diagnostic modalities include plain radiography, computed tomography (CT), magnetic resonance imaging (MRI), radionuclide scans, serum markers, and biopsy.
- Treatment (medical/surgical)
  - Treatment of thymoma includes complete surgical resection. Patients with larger malignant tumors (>8 cm) often receive neoadjuvant chemotherapy, and patients with Masaoka Stage III or IV often receive comprehensive treatment with chemotherapy, radiotherapy, and surgery. Treatment of MG includes immunosuppression with prednisolone, cyclosporine, and azathioprine; rituximab and cyclophosphamide for severely drug-resistant patients; cholinesterase inhibitors such as pyridostigmine; plasma exchange; and thymectomy. Treatment of lymphomas includes chemotherapy, radiotherapy, and immune modulators such as rituximab. Treatment of teratomas is surgical resection. Treatment of seminomas is cisplatin-based chemotherapy. For patients suffering from relapse, high-dose chemotherapy with autologous stem cell transplantation is suggested. In general, surgical resection is not performed for relapse due

to the excessive morbidity from the desmoplastic reaction induced by chemotherapy. Treatment of nonseminomas includes chemotherapy and surgical excision for residual disease, given the poor results noted with salvage chemotherapy.

- Outcomes/Prognosis
  - Most patients with thymoma can expect a favorable outcome, while patients with concomitant MG can expect a normal life expectancy with more than 70 percent noting remission or marked improvement in symptoms with oral corticosteroids alone. Patients with early-stage Hodgkin disease can expect five-year survival rates of greater than 90 percent and remission rates of 70 percent. Patients with non-Hodgkin lymphoma have less favorable outcomes; those with low, low-intermediate, high-intermediate, and high risk disease have five-year overall survival rates of 73, 51, 43, and 26 percent, respectively. The five-year survival rate for seminomas is 88 percent, while the survival rate for nonseminomas varies depending on the primary location of the tumor. Five-year survival rates of 45 percent have been noted; for patients with recurrence, the salvage rate is less than 10 percent.

## INTRODUCTION

The mediastinum is a complicated space associated with a variety of malignant and nonmalignant processes. Due in part to the confinement by the taut mediastinal pleurae, disease of this space may progress rapidly, compress vital structures, or be associated with fulminant inflammatory processes in need of surgical intervention. In this regard, "benign" processes such as infection or traumatic injuries of the mediastinum can be significant threats to the patient.

The mediastinum is the space between the thoracic inlet superiorly, vertebral column posteriorly, sternum anteriorly, and diaphragm inferiorly. The lateral borders of the mediastinum are the mediastinal pleurae. With the exception of the lungs, which lie in the pleural space, all contents of the thorax lie within the mediastinum.

It is useful to consider the mediastinum in terms of three compartments that also serve to organize disease processes, which tend to be localized to one compartment or another (Table 17-1).

**TABLE 17-1: Differential Diagnosis by Mediastinal Subcompartment**

| | |
|---|---|
| Anterior mediastinum | Thymic tumors (thymomas, thymic carcinomas, thymic carcinoid, lipomas), cysts (pericardial cysts), germ cell tumors, lymphomas, intrathoracic thyroid tumors, parathyroid tumors, soft tissue tumors (lipomas, liposarcomas, rhabdomyosarcoma, and hemangiomas) |
| Middle mediastinum | Proximal airway tumors, paraganglioma (chemodectoma), bronchogenic cysts, lymphomas, lymphadenopathy (inflammatory or malignant) |
| Posterior mediastinum | Neurogenic tumors, esophageal tumors, esophageal duplication cysts, esophageal diverticula, hiatus hernia, diaphragmatic hernia, neurenteric cysts |

The *anterior–superior mediastinum* contains blood vessels (the transverse aortic arch, innominate artery, origin of the left common carotid artery, innominate veins, and the upper portion of the superior vena cava), peripheral nerves (the vagus, phrenic, and left recurrent laryngeal nerves), as well as the trachea, esophagus, thoracic duct, thymus, and some lymph nodes.

The *middle mediastinum* contains the pericardium and heart, the ascending aorta, junction of the superior vena cava with the right atrium, junction of the superior vena cava and the azygos vein, tracheal bifurcation, mainstem bronchi, proximal pulmonary artery and bifurcation, confluences of the left and right pulmonary veins, phrenic nerves adjacent to the pericardium, and the peritracheal and subcarinal lymph nodes. The middle mediastinum is bordered posteriorly by the pericardium.

The *posterior mediastinum* runs parallel to the vertebral column behind and is bounded anteriorly by the pericardium, inferiorly by the diaphragm, and laterally by the mediastinal pleurae. It contains the descending aorta, azygos and hemiazygos veins, esophagus, thoracic duct, splanchnic nerves, and lymph nodes.

Surgical approaches to the mediastinum differ based on compartment, and the differential diagnosis for clinical phenomena in this irregularly shaped space is often organized based on location (Fig. 17-1).

The risk of malignancy is about two-thirds for anterior mediastinal masses, compared to 15 to 20 percent for posterior mediastinal lesions.[1]

Embryologically, the space arises from the combination of the ventral and dorsal mesenteries of the esophagus. During embryonic life, the dorsal mesoesophagus supports the esophagus, dorsal primitive aortas, and the cardinal veins in addition to lymphatics and both sympathetic trunks. The ventral mesoesophagus contains the lungs, pericardium, and the heart. The penetrating vessels to the esophagus that arise with the mesoesophagus and the direct lymphatic drainage to the thoracic duct (perhaps contributing to the early systemic spread of esophageal cancer) are clinically relevant anatomic findings that relate directly to the embryogenesis of the mediastinum.

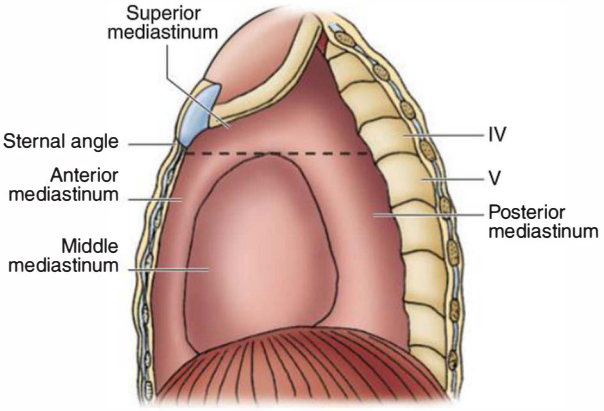



**FIGURE 17-1** Mediastinal compartments. The plane defining the inferior border of the superior mediastinum runs from the sternal angle to the junction of T4 and T5. For the purpose of discussion, the anterior and superior mediastinum are often combined.

# NONMALIGNANT MEDIASTINAL DISEASE

## Mediastinal Infections

### PNEUMOMEDIASTINUM

Pneumomediastinum may derive from injury or perforation of the proximal tracheobronchial tree or the esophagus. It is an emergent condition given the risk of rapid progression to life-threatening mediastinitis with contamination of the confined space lying between the pleurae.

Limited, spontaneous pneumomediastinum (SPM) in the absence of symptoms of systemic infection is generally managed conservatively with bedrest, analgesics, and cough suppressants, as well as prophylactic antibiotics to reduce the possibility of secondary mediastinitis. In general, spontaneous pneumomediastinum does not require surgical intervention. Complications, such as tension pneumomediastinum, delayed pneumothorax, or airway compromise, are rare. The challenge is to differentiate cases of benign spontaneous pneumomediastinum from those associated with more ominous diagnoses such as transmural tears of the esophagus or tracheal injury. The key differentiator lies in the absence of symptoms referable to a finding that is effectively an incidental radiologic observation.[2]

***Outcomes.*** Comparisons of patients with different etiologies of SPM have not been published, nor are there studies analyzing risk factors in patients with SPM. Patients developing pneumomediastinum secondary to barotrauma in the ICU have been noted to have 27 times higher mortality risk compared with other underlying conditions. Ventilator-induced barotrauma is an independent prognostic factor for hospital mortality. Secondary pneumomediastinum resulting from blunt force thoracic trauma has a more favorable outcome in comparison with pneumomediastinum associated with prolonged ventilation, poorly compliant lungs, and subsequent barotrauma.[3]

***Prognosis.*** Mortality rates of 10 and 13 percent have been noted among trauma patients with pneumomediastinum.[2] In ventilator-induced barotraumas, mortality rates of 55 and 65 percent have been noted in patients with mediastinal emphysema and pneumothorax, respectively.[3]

### ACUTE MEDIASTINITIS

***Treatment.*** Acute mediastinitis is a surgical emergency for which medical therapies serve an adjunctive role only. Surgical correction of the source of the mediastinal contamination, debridement of infected tissues, and, in certain cases, diversion of the esophagus are the keys to a successful outcome. Antibiotic administration, fluid resuscitation, invasive monitoring, and hemodynamic support are principal nonsurgical measures.

***Outcomes.*** Outcomes are dependent on host risk factors that might contribute to the development of deep surgical site infections, including obesity, diabetes mellitus, ischemia (following the use of bilateral internal thoracic artery grafts, for example), advanced age, female sex, chronic lung disease, active smoking, prolonged mechanical ventilation, the use of steroids, and preoperative hospital stay longer than 5 days.[1]

***Prognosis.*** Postoperative mediastinitis occurs in 1 to 3 percent of patients undergoing median sternotomy, and its associated mortality has been reported to be as high as 40 percent.[2]

### CHRONIC MEDIASTINITIS

Once symptoms for both granulomatous and fibrosing (also known as sclerosing) mediastinitis have ensued as a result of obstruction and compression of mediastinal structures, no medical therapy has been shown to be of uniform benefit, nor have surgical corrections been met with much success. Antifungal agents, steroids, and immunosuppressive agents are used for both etiologies, while studies have shown that tamoxifen can be effective in the medical treatment of fibrosing mediastinitis. The effectiveness of steroid therapy has been controversial.[4]

### SUPERIOR VENA CAVA OBSTRUCTION

***Treatment.*** Treatment is directed at either symptomatic alleviation or the underlying cause. First-line therapy is classically surgery or stenting procedures. Traditional medical treatment has included systemic steroids (prednisolone or dexamethasone) and diuretics. For patients with SVC obstruction due to malignancy, chemoradiotherapy is used. Steroids are generally given in conjunction with radiotherapy

because of the concern for radiation-induced edema. Radiotherapy can take two to four weeks to show effect and has significant rates of complications, including radiation-induced esophagitis and pneumonitis. A systematic review by Rowell et al. found complete relief of the symptoms of SVC obstruction in 77 percent of patients with small-cell lung cancer and 60 percent with non–small-cell lung cancer at two weeks.[5] For patients with SVC obstruction due to intravascular thrombus associated with an indwelling catheter, removal of the catheter and anticoagulation is standard. However, the efficacy of short- or long-term anticoagulation therapy is unclear. Although thrombolytic agents have been used effectively in patients with vena caval thrombosis, most experts recommend anticoagulation after thrombolysis (to prevent disease progression and recurrence) and aspirin after stent placement in the absence of thrombosis.

***Outcomes.*** Outcomes are dependent on the underlying cause. Despite treatment with radiotherapy or chemotherapy, some patients fail to respond and symptoms persist. Systematic analysis noted a 17 percent recurrence rate.[5]

***Prognosis.*** Reported recurrence rates are 18 to 20 percent. Recurrence can be due to either persisting tumor mass or SVC thrombosis.[6] In some patients, SVC obstruction may relapse after a period of time despite a good initial response.

### CASTLEMAN DISEASE

Castleman disease or benign B-cell hyperproliferation, often associated with HIV infection, involves lymphadenopathy within the mediastinum.

***Treatment.*** Surgery is the mainstay of treatment for both multicentric and unicentric disease. For multicentric Castleman disease, variable treatment modalities have been used, including lymphoma-based chemotherapeutic regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), immunotherapies such as interferon alpha, and monoclonal antibodies such as rituximab. For unicentric Castleman disease, chemotherapy is usually unnecessary.[7,8] For locally advanced, unresectable, unicentric Castleman disease, neoadjuvant radiotherapy of 40 to 50 Gy is used to facilitate radical resection. No randomized controlled trials have been conducted to definitively characterize optimal treatment because of the infrequency of the diagnosis; case reports are predominant in the literature.[7,8]

***Outcomes.*** For unicentric disease, complete resection has been reported to be curative and recurrence is rare. For multicentric disease, outcomes are significantly worse, but the true difference is unclear because treatment strategies vary.[9]

***Prognosis.*** For patients with resectable unicentric disease, treatment is curative. For patients with multicentric disease, the median survival is two to three years.[9]

## MEDIASTINAL DISEASE BY COMPARTMENT

### Anterior Mediastinal Masses

The anterior–superior compartment is the most common site for mediastinal masses, and the majority of these masses are malignant. Lymphomas, thymomas, and germ cell tumors are the leading diagnoses in this compartment. Less frequently, masses may be of endocrine origin, lipomas, infections, vascular malformations, or other rare neoplasms.

Characteristics of the masses on imaging may suggest a diagnosis, but a complete history and physical examination add valuable information. Symptomatic patients are more likely to have a malignant mass than asymptomatic patients. Constitutional symptoms suggest lymphoma or an endocrine tumor. Weakness with repetitive muscle use suggests myasthenia gravis (MG) with associated thymoma. Cardiothoracic symptoms such as chest pain, cough, dysphagia, or hoarseness suggest compression by the tumor. On physical examination, findings of neck masses, lymphadenopathy, evidence of SVC syndrome, or testicular masses all add valuable information to the working diagnosis. Laboratory evaluation for endocrine disease, paraneoplastic syndromes, or tumor markers such as beta human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP) may have a role. The standard imaging of a chest x-ray and CT scan may be supplemented with nuclear imaging by SESTAMIBI or positron emission tomography (PET) scanning for endocrinologically active tumors such as thyroid masses, parathyroid adenomas, and thymic carcinoid.

The role of biopsy for anterior mediastinal masses, particularly thymomas, is controversial because of the possibility of tumor seeding. In addition, even with CT or ultrasound guidance, the fine-needle aspiration (FNA) may produce a false-negative biopsy. Finally, the pathologist may not be able to differentiate thymoma from lymphoma on the basis of an FNA sample. Core biopsy allows more tissue for evaluation, and despite earlier concerns about the use of cutting needles for mediastinal biopsies, it is now generally accepted as safe. Surgical biopsy, which can often be obtained through a small anterior mediastinotomy (Chamberlain incision), permits accurate diagnosis when clinical history, radiographs, and percutaneous biopsy are not determinant.

### LYMPHOMA

Lymphomas are the most common neoplasm of the mediastinum, although primary mediastinal lymphomas are rare and account for less than 10 percent of lymphomas. The most common types of lymphomas found in the mediastinum include Hodgkin, non-Hodgkin, and lymphoblastic lymphomas. B-cell lymphomas arise when errors occur during critical processes of B-cell development, such as V(D)J recombination, somatic hypermutation, and class switch recombination, which are involved in light- and heavy-chain formation and DNA modification. Largely curable, Hodgkin lymphoma (HL) is most common in the third decade of life

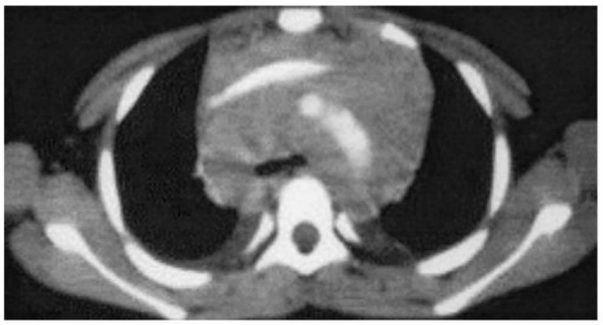


**FIGURE 17-2** Computed tomography of a lymphoma in the anterior mediastinum.

but has a bimodal peak at 15 to 34 years and over 60 years. Hodgkin lymphoma outcomes are predicted according to the International Prognostic Score. The most common histologic types in order of incidence are classical Hodgkin lymphoma (nodular sclerosis, mixed cellularity, lymphocyte-predominant, and lymphocyte-depleted types) and nonclassical Hodgkin lymphoma (nodular lymphocyte-predominant). Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies seen at all ages but is most concentrated in patients greater than 50 years of age. In addition, patients with HIV/AIDS are at increased risk for NHL. Lymphoblastic lymphoma is a rare and aggressive neoplasm of immature B-cells committed to the B-cell or T-cell lineage that primarily affects children but can also be seen in adults with a median age of 39 years (Fig. 17-2).

***Treatment.*** Patients with early-stage Hodgkin lymphoma are treated with two to four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by involved-field radiotherapy (IF-RT) with 30 Gy.[2-5] In advanced HL, administration of six to eight cycles of chemotherapy optionally followed by radiotherapy of residual disease is the treatment of choice. Recently bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) are being used, particularly for high-risk patients. An optimal treatment regimen for Hodgkin lymphoma has not been determined; at this time, chemotherapy alone or various combinations of chemotherapy and radiotherapy are associated with high overall survival rates. Meta-analysis has suggested chemotherapy plus radiotherapy is superior to chemotherapy alone, although side effects and the development of secondary malignancies in younger patients continue to be a concern.[4-5] Currently, ABVD remains the gold standard of chemotherapy although increasing data note that using the aggressive BEACOPP regimen has improved survival in advanced stages. Mustargen, oncovin, procarbazine, and prenisone (MOPP) and MOPP/ABVD have been replaced due to concerns for toxicity, while European groups are increasingly using BEACOPP.[10]

NHL treatment strategies are based on histology and World Health Organization staging criteria. The current standard of care for first-line chemotherapy is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). For patients with follicular NHL or diffuse large B-cell lymphoma, the addition of anti-CD20 rituximab is considered standard therapy. Monoclonal antibodies and integration of radioimmunotherapy as part of initial therapy are being investigated at this time.

***Outcomes.*** The five-year survival rate for patients with early-stage Hodgkin lymphoma has consistently been greater than 90 percent, with complete remission occurring in more than 70 percent.[11] ABVD-based treatments have noted five-year recurrence rates of 61 to 66 percent and five-year overall survival rates of 73 to 83 percent. Unfortunately, 30 to 40 percent of patients with advanced stage Hodgkin lymphoma experience treatment failure requiring salvage high-dose chemotherapy or autologous stem cell transplantation.[12] Patients presenting with mediastinal manifestations, despite the lack of a unified system of categorization, are defined as high risk according to most standards. For patients older than 60 years, treatment options have been limited due to increased susceptibility to the toxic effects of intensive therapy and often comorbid conditions.[13]

Patients with low-grade NHL are likely to respond to standard treatment regimens with subsequent relapse, although the duration of relapse decreases with each subsequent treatment. For patients with low-grade NHL, autologous bone marrow transplantation can lead to complete remission although long-term follow-up is required for determination of cure rate. For patients with intermediate- to high-grade NHL that does not go into remission or relapse, the prognosis is poor.[15]

***Prognosis.*** In accounting for all stages of HL, the five-year survival rate is greater than 90 percent. However, more patients die from treatment-related complications than from progressive or recurrent lymphoma. Secondary malignancies occur at roughly one percent per year for 30 years after treatment and are particularly high among young women (age <30 years) who received thoracic radiation. Between 30 and 40 percent of these women will develop breast cancer in the 25 years posttreatment.[14] In addition, cardiac disease due to radiotherapy and chemotherapy has been noted to be significantly increased for more than 25 years posttreatment, with increased rates of coronary artery disease, myocardial injury, valvular disease, and pericardial fibrosis.

For diffuse large B-cell lymphoma, the original International Prognostic Index (IPI) created in 1993 is still used to predict outcomes for patients. For patients in low, low-intermediate, high-intermediate, and high risk categories, the five-year overall survival rates are 73, 51, 43, and 26 percent, respectively. A revised version was created by Sehn et al. to account for the introduction of rituximab. For patients in very good, good, and poor risk categories, the four-year estimated progression-free and overall survival rates are >90, >80, and >50 percent, respectively. Currently, the original IPI remains the validated and definitive measure for assessing risk.

## THYMOMA

***Epidemiology and Pathology.*** The thymus plays an important role in immunologic development in early life and then begins to involute in adolescence. Thymic tumors are rare in children, and are most common in middle-aged adults. About 20 percent of anterior mediastinal masses are of thymic origin. The term thymoma refers to neoplastic growth of the thymic epithelial cells. The vast majority of thymomas are well-encapsulated neoplasms that are considered benign and cause clinical disease as a result of compression of surrounding structures or through a variety of neoplastic syndromes. There are two main types of malignant thymomas that are histologically and biologically different. The first type is histologically identical to a benign thymoma except it has violated its capsule and is capable of invasion of surrounding tissues or distant metastasis. Despite this spread, the tissue lacks features commonly associated with malignancy including increased mitotic activity. The second type is a thymic carcinoma and is histologically different from the encapsulated thymomas. These tumors are rare and aggressive, and they have a poor prognosis. The most frequently used classification system is one based on the scale developed by Masaoka and colleagues in 1981. This system stages the tumor on the basis of histologic examination of the capsule and does not consider the size of the tumor. An intact capsule is stage I, transcapsular invasion with or without invasion of adjacent tissues is stage II, invasion of adjacent organs is stage III, and involvement of the pleura, pericardium, or distant metastasis is stage IV. The World Health Organization has developed a staging system based on tumor cell type.

***Clinical Presentation.*** The clinical presentation of thymomas varies. The majority of patients are asymptomatic with an incidentally discovered mass. Some patients may be symptomatic due to local compression or invasion, whereas others have a mass discovered during an evaluation for paraneoplastic syndromes. The most common association is thymoma with MG. About half of patients with thymoma have MG, but the vast majority of patients with MG do not have thymoma.

***Investigation.*** Classic thymomas have a characteristic appearance on chest computed tomography; they are smooth contoured masses that are well defined and encapsulated, and some may have cystic changes. Invasion of an encapsulated mass into nearby structures suggests a malignant thymoma. Thymic carcinoma is characterized by irregular borders, and metastases are frequently present at the time of presentation.

All patients with thymoma should be evaluated for MG. A careful history and physical examination looking for progressive muscle weakness with repetitive exertion should be performed. The role of preoperative biopsy remains controversial. The main concern is seeding the tumor along the needle track or into the mediastinum as drop metastases. In addition, small amounts of tissue or specimens obtained by FNA may be insufficient to distinguish thymoma from lymphoma. In the absence of invasion into local structures, resection alone is generally offered. For a larger mass, a careful biopsy may assist with operative planning or neoadjuvant therapies (induction chemotherapy or chemoradiation).

***Treatment.*** The treatment of choice in a patient with thymoma is removal of the entire thymus gland. An expanding number of surgical approaches exist for resection. The traditional median sternotomy (partial or full) provides ideal exposure and a minimum of morbidity. Recently, smaller well-encapsulated tumors have been resected via camera-guided minimally invasive approaches including robot-assisted thymectomy. For larger tumors or tumors with local invasion, an anterior thoracotomy or even a bilateral anterior thoracotomy with transverse sternotomy (clamshell incision) is employed. Larger malignant tumors (>8 cm) may benefit from neoadjuvant chemotherapy to improve the chances of complete resection. Debulking operations are unlikely to provide significant benefit and should generally not be performed. An exception occurs when bilateral phrenic nerve entrapment is found intraoperatively. To avoid bilateral vocal cord paralysis, residual tumor adjacent to one recurrent laryngeal nerve may be left in hopes that postoperative radiotherapy or chemotherapy may provide local control.

The Masaoka and WHO staging systems both correlate with prognosis and outcomes. Stage-specific overall survival for patients with stage III cancers is significantly lower than that for patients with stage I or II disease. However, in patients with stage III disease who undergo successful, microscopically margin-negative (R0) surgical resection, five-year survival rates approach that of patients with stage I disease (80 vs. 75 percent for stage III disease).[16] For patients with more advanced disease (stage III or greater), complete surgical extirpation (including contiguous resection of lungs, pericardium, and/or great vessels) with negative margins is more challenging. Most patients with early-stage disease undergo R0 resection, but only 50 to 60 percent of patients with stage III thymomas taken directly to surgery actually achieve microscopically negative margins. If not, additional therapy as an adjunct to surgery plays a role.[16]

A reasonable approach how and best to use multidisciplinary care is based on the National Comprehensive Cancer Network Guidelines (version 2.2011) for thymic malignancies.[17] Patients with stage I to IIB disease undergo immediate surgical resection, with adjuvant radiotherapy reserved for pathologic capsular invasion or microscopically positive margins (R1 resection). If the final pathology reveals a thymic carcinoma, adjuvant chemotherapy should also be included. Patients who present with stage III to IVA disease proceed to surgery if deemed eligible for resection by a multidisciplinary team of experts. However, if it seems unlikely that R0 resection can be achieved initially, an induction chemotherapy or chemoradiation should be used, followed by restaging and consideration of surgical resectability. If eligible for resection, the patient proceeds to surgery and adjuvant therapy can be considered as described for the early-stage patients; if the thymoma is unresectable, definitive chemoradiation is performed.[17]

## MYASTHENIA GRAVIS

Initial treatments for MG are the acetylcholine (ACh) esterase inhibitors, such as pyridostigmine, which inhibit the breakdown of ACh at the neuromuscular junction, thus increasing the availability of ACh to stimulate ACh receptors (AchR) and facilitate contraction. AChR antibody-positive early-onset patients with generalized MG and insufficient response to pyridostigmine therapy should be considered for thymectomy, ideally within one year of disease onset. Patients with associated thymoma should have a thymectomy. In general, patients with MG and thymomas do not respond as well to thymectomy as do patients with MG without thymomas.[18] In addition, immunosuppressive medication should be considered in all patients with progressive MG symptoms. Patients are usually started on prednisolone, as well as bisphosphonate, antacids, and azathioprine to prevent osteoporosis and gastrointestinal complications. Observational studies over the past 30 years have noted remission or marked improvement in 70 to 80 percent of patients with MG treated with oral corticosteroids, usually prednisolone.[19] For patients intolerant of this regimen, treatment with another immunosuppressive drug should be considered. Short-term immunotherapy, specifically plasmapheresis and intravenous immunoglobulin (IVIG), has been noted to have short-term benefit although there are no adequate randomized controlled trials to quantify its benefit. Retrospective studies have shown that plasmapheresis is valuable in lessening symptoms during initiation of immunosuppressive drug therapy, during an acute crisis, and as a short-term treatment in severe cases to induce remission and in preparation for surgery. However, there is currently insufficient evidence on the efficacy of plasmapheresis in the treatment of myasthenic crisis or MG before thymectomy. IVIG has been noted to have a positive effect in the acute phase of MG. However, in mild or moderate MG, no significant different in efficacy between IVIG and placebo, or between IVIG and methylprednisolone, was found at 6 weeks. Currently, there is not sufficient evidence for definitive selection of second-line drug therapy. In general, azathioprine may be used if insufficient remission is achieved with steroids, followed by cyclosporine and mycophenolate, while rituximab and cyclophosphamide are used only in severely drug-resistant patients. Azathioprine is recommended with steroids to allow tapering of the steroids to the lowest dose possible. Its onset of therapeutic response may take 4 to 12 months, and its maximal effect is at 6 to 24 months. Cyclophosphamide, an alkylating agent, is also effective.

## GERM CELL TUMORS

***Epidemiology and Pathology.*** Both seminomas and nonseminomas, including teratomas, occur in the mediastinum and compromise approximately 20 percent of anterior mediastinal masses. All forms of these tumors have a peak incidence in young adults. These tumors are thought to be the result of pluripotent germ cells that fail to migrate from the mediastinum to the gonads during early development.

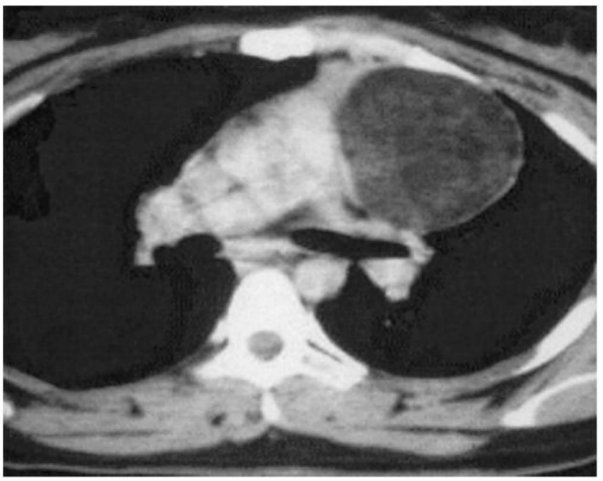


**FIGURE 17-3** Computed tomography of a mediastinal germ cell tumor.

Mediastinal germ cell tumors are pathologically identical to the gonadal germ cell tumors. Extragonadal germ cell tumors are rarely primary tumors, and the mediastinum is a frequent site of metastasis. The other common extragonadal sites are the retroperitoneum and the brain. Therefore, any mediastinal germ cell tumor, except mature teratomas, should prompt a search for an occult primary in the gonads, retroperitoneum, or brain (Fig. 17-3).

## SEMINOMAS

Seminomas are rare, occur exclusively in men, and are generally malignant but highly responsive to treatment. The tumors are composed of cells that appear similar to spermatogonia but are nonfunctional. Most patients are symptomatic at time of presentation. Some of these tumors contain syncytiotrophoblastic cells that secrete β-hCG, although serum levels may be undetectable. These tumors never secrete AFP.

***Treatment.*** The established treatment according to the International Germ Cell Cancer Collaborative Group (IGCCCG) criteria consists of three to four cycles of cisplatin-based chemotherapy, either four cycles of neoadjuvant etoposide and cisplatin, or three cycles of bleomycin, etoposide, and cisplatin (BEP). These regimens have durable response rates of 81 to 92 percent and favorable toxicity profiles.[20,21] For intermediate seminomas, defined as those tumors with nonpulmonary visceral metastasis, the standard regimen is four cycles of BEP.[22] For patients who relapse after initial chemotherapy, standard doses of three-drug combinations based on ifosfamide and cisplatin or high-dose chemotherapy with autologous stem-cell support are used. No randomized controlled trials have been conducted to compare treatment modalities, but improved outcomes have been noted with paclitaxel, ifosfamide, and cisplatin, plus either vinblastine or etoposide.[23] Post-chemotherapy

surgical resection of seminomas is technically difficult due to the desmoplastic reaction induced by chemotherapy and in general is not done.[24]

***Outcomes.*** A large retrospective study by Bokemayer et al. from 11 United States and European cancer centers noted no significant difference in progression-free and overall survival between mediastinal and retroperitoneal seminomas. Five-year objective remission rate (ORR) and overall survival rate were 92 and 88 percent, respectively. The presence of nonpulmonary visceral metastases significantly decreased overall survival, with five-year progression-free and overall survival rates of 67 and 72 percent, respectively.[22]

## NONSEMINOMAS

Nonseminomas arise from embryonal tissue and include embryonal carcinoma, teratocarcinoma, choriocarcinoma, yolk sac tumors, and benign teratomas. If a tumor has components of both seminoma and embryonal tissue it is called a mixed germ cell tumor and is included in this category as well. With the exception of benign teratoma, these tumors are more frequent in men, are almost always malignant, and are more likely to have metastasized to nearby tissue and lymph nodes than seminomas. Histologically, many of these tumors contain either yolk sac cells that secrete AFP, syncytiotrophoblastic cells that secrete β-hCG, or both. Most patients will have elevated serum levels of these hormones, which are useful for both diagnosis and following response to treatment.

Teratomas are the most common of the germ cell tumors and have a different epidemiology, histology, and biology than the others. These tumors occur equally in men and women, are generally benign and consist of at least two of the three embryologic layers: endoderm, mesoderm, and ectoderm. A mature teratoma has differentiated into mature somatic structures such as skin, bone, teeth, fat, and epithelial tissue. Less than one percent undergo malignant transformation. An immature teratoma also contains tissue from multiple embryonic layers, but the tissues are similar to fetal tissue and are at greater risk of being malignant. Benign mature teratomas should be surgically removed and pathologically examined for evidence of occult cancer within the tumor (Fig. 17-4).

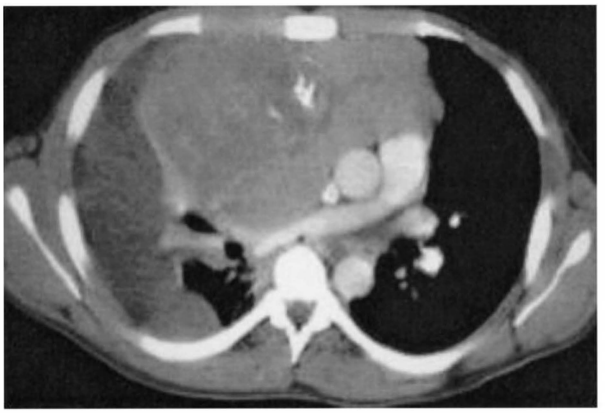


**FIGURE 17-4** Computed tomography of a mediastinal teratoma containing a well-differentiated structure (tooth).

***Clinical Presentation.*** Benign teratomas often come to attention either through compression of nearby structures, or through a connection with a bronchus that leads to expectoratation of contents of the teratoma. Seminomas and nonseminomatous tumors may present with symptoms of local compression or with symptoms of systemic endocrine changes such as gynecomastia. Nonseminomatous tumors have a known association with Klinefelter syndrome.

***Investigation.*** Any man with an anterior mediastinal mass should have serum β-hCG and AFP levels drawn. In addition, once the diagnosis of germ cell tumor is made, a thorough investigation for an occult primary tumor and other metastases should be undertaken, including physical examination of the testes or ovaries for masses, and imaging of the retroperitoneum and brain.

***Treatment.*** Treatment consists of four cycles of BEP followed by surgical resection. After cisplatin-based chemotherapy for primary mediastinal nonseminomatous germ cell tumors (PMNSGCT), a residual mass in the mediastinum is usually present; only infrequently does pathology demonstrate complete tumor necrosis. Surgical removal of residual disease after chemotherapy has been advocated due to the poor results noted with salvage chemotherapy. Currently, using etoposide, ifosfamide, and cisplatin (VIP) is being investigated for initial chemotherapy due to the significant pulmonary toxicity and therapeutic equivalency of BEP.[25]

***Prognosis.*** PMNSGCT, although histologically identical to their more common testicular counterparts, have a distinctly worse prognosis and therefore have been designated as poor-risk nonseminomatous germ cell tumors along with other subsets of testicular nonseminomatous germ cell tumors. In addition, the presence of nonpulmonary metastases, β-hCG >50,000, AFP >10,000, or LDH >10-times normal all suggest a poor prognosis.[22] Patients with retroperitoneal or gonadal primary sites have better prognosis than patients with primary mediastinal GCT. With the incorporation of four cycles of cisplatin-based chemotherapy, retrospective analyses have noted ORR of 40 to 80 percent and a survival rate of 30 percent. Two prospective studies of 31 and 41 patients noted a long-term survival of greater than 50 percent after cisplatin-based chemotherapy plus surgery, while Bokemeyer et al. noted a long-term survival rate of 48 percent.[26]

***Outcomes.*** For mediastinal nonseminomas, prognosis is poor compared to primary gonadal and retroperitoneal nonseminomas, with five-year overall and progression-free

survival of 45 and 44 percent, respectively. For patients with recurrence, the salvage rate has been noted to be less than 10 percent with cisplatin-based chemotherapy. Consequently, surgical resection plays an important role in salvage treatment when no effective chemotherapy is available.[25]

## THYMOLIPOMA

This rare tumor is a neoplasm of the thymic fat and is usually benign. Its classic appearance on chest imaging is a large mass of fat with areas of normal thymus tissue scattered throughout. This tumor does not invade surrounding tissue, but can grow quite large and compress surrounding structures. Large tumors should be resected for this reason.

## THYMIC CARCINOID

***Treatment.*** Surgical resection is the primary treatment modality for thymic carcinoids with additional chemotherapy and radiotherapy used as needed for advanced disease. Due to the relative rarity of the disease and lack of randomized controlled trials, standardized treatment has not been established. For patients with early-stage disease, chemotherapy either before or after adjuvant radiotherapy deserves strong consideration considering the aggressive nature of the disease (Fig. 17-5). For patients with locally advanced disease, neoadjuvant treatment with chemoradiation may offer the potential for downstaging and increased resectability. There are no studies investigating the use of neoadjuvant chemoradiation followed by aggressive resection, but there are case reports establishing feasibility.[18] For patients with advanced thymic carcinoids that cannot be completely resected, neoadjuvant or adjuvant systemic treatment is required, often in combination with radiotherapy. A case report by Filosso et al. describes treating a patient with bulky thymic carcinoid with 45 Gy radiation concurrently with four cycles of cisplatin and etoposide; complete resection was achieved.[27] Cisplatin-based regimens, such as cisplatin, adriamycin, and cyclophosphamide (PAC), are used most often. Evidence supporting radiotherapy in the adjuvant, neoadjuvant, or definitive setting is limited; case series and case reports suggest that the addition of postoperative radiotherapy may improve local control following complete resection. Tiffet et al. published a case series of 12 patients, of whom nine patients had an R0 resection. Three of the nine patients received adjuvant radiotherapy, and none had a local recurrence. Six of the nine patients did not receive adjuvant radiotherapy, and four had a local recurrence.[28] Surgery followed by radiation offers a reasonable probability of local control, but these patients remain at high risk for metastatic disease. A multimodality approach to treatment is worth considering. Targeted molecular therapy is increasingly being used; inhibitors of c-kit, epidermal growth factor receptor (EGFR), and various receptor tyrosine kinases have been reported in small studies with mixed results.[29]



**FIGURE 17-5** Computed tomography of a thyroid carcinoma in the superior mediastinum.

***Prognosis.*** Thymic carcinoids have a poor prognosis, are locally aggressive, and have demonstrated metastatic rates ranging from 40 to 82 percent.[30] Completeness of resection is a strong prognostic indicator. In the largest series to date, overall five- and 10-year survival was 28 and 10 percent, respectively.[18]

***Outcome.*** Outcome data are limited due to the small series of patients studied; relapses or progressive disease can be expected to occur in 10 to 30 percent of patients. In 20 to 30 percent of these patients, objective remissions can be achieved by cisplatin-based regimens after relapse-free intervals. Approximately 50 percent of patients with an advanced malignant thymoma or thymic carcinoma will be candidates for second-line treatment.[18]

## THYROID

Substernal goiter is the most common mass in the superior mediastinum and can be found in up to 20 percent of goiter operations. These masses are generally benign. Most patients come to attention for treatment of a neck mass that extends substernally. The extent of the mass can be determined by CT scan or nuclear imaging. Complications from the mass include compression of the trachea or esophagus, compression of the recurrent laryngeal nerve, or compression of the neck veins impeding drainage of blood from the head and neck. Surgical treatment is indicated if there is compression of important structures and if radioactive iodine treatment fails. Rarely, a partial median sternotomy is required if removal of the substernal goiter cannot be accomplished through the traditional cervical approach.

### PARATHYROID

Ectopic parathyroid glands may be located in the mediastinum, including the pericardium and the recurrent laryngeal nerve. Patients come to attention because of hyperparathyroidism, and may have had a failed parathyroidectomy in the neck. Ninety-nine percent of parathyroid adenomas are benign, but surgery is indicated to cure the hyperparathyroidism. The surgical approach will be dictated by location of the active gland, which is determined by nuclear imaging; most can be accessed through a cervical incision. Intraoperative and postoperative measurements of parathyroid hormone can assist with determining whether all affected glands have been removed. On gross examination, parathyroid adenomas will be enlarged but well encapsulated. In contrast, parathyroid carcinoma is characterized by a larger-than-expected firm gland that is unencapsulated and adheres to surrounding tissues.

## Middle Mediastinal Masses

Because the categorization of compartments of the mediastinum does not reflect true anatomic divisions, any of the masses of the anterior or posterior mediastinum can present as a middle mediastinal mass. However, the most common masses of the middle mediastinum are benign cysts that form during early development associated with the pulmonary system, pericardium, or esophagus. Mediastinal lymphadenopathy may appear as a mass in this compartment and may be related to primary tumors such as lymphoma, lymphatic metastases of primary lung or esophageal cancers, or other processes related to infection or inflammation. In addition, large vessels in the mediastinum may develop aneurysms that can appear as mediastinal masses on chest imaging. Using intravenous contrast with CT imaging or performing angiography will identify these structures as vascular.

Symptoms are common with masses in this compartment as cysts may cause compression or obstruction of important structures, or may become infected. Children are symptomatic more often than adults because of their smaller intrathoracic volume. Laboratory tests are generally normal. After the initial chest x-ray and CT scan of the chest, there is often a role for transthoracic or transesophageal ultrasound. Ultrasound may further characterize whether the cysts are simple or complex, and biopsies or drainage may be accomplished using this technology.

### BRONCHOGENIC CYSTS

Bronchogenic cysts are formed during one of two abnormalities of fetal development. Most commonly, they form as aberrant budding from the foregut's ventral surface and are located posterior to the carina or a main stem bronchus. Otherwise, they form as abnormal budding from the tracheobronchial tree. They are usually simple cysts, lined with respiratory epithelium, filled with serous or mucus fluid, and surrounded by smooth muscle and cartilage that limit their growth. Generally they are discrete and do not communicate with the respiratory tree, but communication is possible and it increases the risk of the cyst becoming infected. Because of their limited intrathoracic space, neonates are more likely to present symptomatically than older children or adults with cysts of the same size. Cysts in adults are often discovered incidentally. These cysts are generally benign, although there is a small risk of malignant transformation.

Evaluation includes a CT scan of the chest to further characterize the cyst. A simple fluid-filled cyst in the expected location is classic. Evidence of a septated cyst or one with aberrant features needs further evaluation. An air–fluid level suggests communication with the tracheobronchial tree or infection. If there are concerns about a cyst, transbronchial biopsy and aspiration of cyst contents for pathologic analysis is an option prior to surgery.

***Treatment.*** Traditionally, all cysts were removed via thoracotomy for three main reasons: (1) a substantial percentage of asymptomatic patients eventually become symptomatic, (2) if the cyst becomes infected, the formation of adhesions complicates removal, and (3) there is a small but finite risk of malignant transformation. Currently, many cysts can be removed by minimally invasive techniques such as video-assisted thoracic surgery, which reduces operative morbidity. In addition, small simple cysts that are asymptomatic may be observed and removed if symptoms develop.

If the cyst is removed surgically, the entire cyst should be removed. Any remnant cyst wall that cannot be removed should be cauterized if possible to avoid recurrence. For a poor surgical candidate, the cyst can be drained through a transbronchial aspiration, and then filled with alcohol or bleomycin to promote fibrosis and prevent reaccumulation of fluid.

### PERICARDIAL CYSTS

Pericardial cysts are the second-most common type of mediastinal cysts and form during embryologic development as a discrete cyst composed of a single layer of mesothelial cells. They are most commonly located at the right costophrenic angle and are often asymptomatic. Rarely, pericardial cysts rupture into the pericardial cavity and cause cardiac tamponade. Even more rarely, these cysts grow to a size that impairs the right ventricular outflow tract, causing critical hypotension and death. If patients are asymptomatic, the cyst may be observed. If patients are symptomatic, the cyst can be treated by aspiration under fluoroscopy, or operative decompression. Because of the typical location of the cysts, minimally invasive techniques will generally be useful.

### ESOPHAGEAL DUPLICATION CYSTS

Esophageal duplication cysts are the least common of the mediastinal cysts. Whereas bronchogenic cysts bud from

the ventral aspect of the developing foregut, esophageal duplication cysts bud from the dorsal aspect. The cyst lining is composed of acid-secreting digestive tract epithelium, and the cyst may be outside of the esophageal wall or encompassed within it. Rarely, the duplication cyst buds from dorsal foregut under conditions that place it in proximity to the developing spinal cord, creating a "neurenteric cyst" that integrates both enteric and neural tissue in the cyst structure.

The clinical presentation of patients with symptomatic esophageal cysts includes chest pain or dysphagia as a result of esophageal compression. Possible complications of esophageal cysts include infection, esophageal perforation, and hemorrhage. Patients with neurenteric cysts may also have neurologic symptoms related to involvement of the spinal cord. Investigation of a suspected esophageal cyst is by chest CT and endoscopy. If a neurenteric cyst is suspected, an MRI may offer better imaging of any spinal cord involvement.

Treatment is surgical resection of the entire cyst and is offered to all patients who are appropriate surgical candidates. In contrast to bronchogenic cysts that may be observed, esophageal duplication cysts have a serious risk of complications, making surgical resection the standard of care. A neurenteric cyst resection involves coordination between thoracic surgeons and neurosurgeons.

## Posterior Mediastinal Masses

The posterior compartment contains the paravertebral gutters and masses in this location are most often of neurogenic origin. Other masses include esophageal cysts, including neurenteric cysts, esophageal malignancy, and diaphragmatic hernia. In children, this compartment is by far the most common site for mediastinal masses, which are likely to be symptomatic and malignant. In adults, masses in this compartment are less common than anterior mediastinal masses, and they are more likely to be benign.

### NERVE SHEATH TUMORS

Nerve sheath are generally of two types: the more common schwannomas and less common neurofibromas. Schwannomas, also known as neurilemmomas, are benign tumors of the Schwann cells that are firm and encapsulated. They grow slowly, are generally only found in adults, and are unlikely to undergo malignant transformation into neurofibrosarcomas. In contrast, neurofibromas are slow-growing tumors of the peripheral nerve sheath, involve multiple cell types including Schwann cells and fibroblasts, and are soft and not encapsulated. They are associated with neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease. Malignant peripheral nerve sheath tumors may occur spontaneously or as a result of transformation of a benign tumor. Risks for malignant transformation include NF1 or prior irradiation of the area. These tumors are poorly differentiated sarcomas and may invade locally as well as spread hematogenously.

Patients with these tumors present with radiculopathy and neurologic symptoms from spinal cord compression. Patients with malignant tumors may have episodes of hypoglycemia arising from the release of an insulin-like hormone from the tumor. Multiple neurofibromas are a strong indicator of underlying NF1 disease. MRI may offer additional information over the CT images.

Benign peripheral nerve sheath tumors are treated surgically through either posterior thoracotomy or a minimally invasive technique. The primary treatment of malignant peripheral nerve sheath tumors continues to be surgical resection, but active research into possible chemotherapeutic treatments holds promise for these patients.

### NEUROBLASTOMA

Neuroblastoma is a congenital malignancy of neural crest cells that arises from the adrenal medulla or sympathetic ganglia. Tumors may develop anywhere along the spine, and approximately 20 percent are in the posterior mediastinum. The tumor is a malignancy of infants and young children, with most patients being diagnosed before five years of age. It is the most common extracranial solid tumor in children. The clinical course is varied and spontaneous remission is possible, but aggressive disease is not uncommon. Extraadrenal tumors, especially posterior mediastinal tumors, tend to be less aggressive. Children diagnosed before 12 months of age have better survival at all stages of disease than do older children, and they are more likely to undergo spontaneous regression.

Clinical presentations vary, and most children present with a palpable mass in the abdomen. For children with a posterior mediastinal mass, respiratory distress may be prominent. The tumors often have neuroendocrine activity, and diarrhea may occur if the tumor is releasing vasoactive intestinal peptide. A paraneoplastic syndrome associated with neuroblastoma is opsoclonus myoclonus syndrome, also called "dancing eyes and feet" syndrome, and some children have persistent neurologic deficits after treatment. Both diarrhea and opsoclonus myoclonus syndrome are rare, but are associated with improved prognosis.

Neuroblastoma often appears on imaging as a paravertebral shadow that may contain calcifications. Specifically in the posterior mediastinum, the tumor may cause splaying of the posterior ribs that is visible on chest x-ray. Evidence of vertebral pedical erosion may be present and suggests that the tumor may have extended into the spinal cord. Chest CT is the standard preoperative imaging, but MRI may be valuable if there is a concern about central nervous system involvement. PET scans offer useful information about presence of metastases.

The treatment for neuroblastoma is influenced by the biologic features of the tumor, the age of the child, and the stage of disease. Treatment protocols have been developed and generally follow the schema of surgery alone for

low-risk disease; surgery with chemotherapy for moderate-risk disease; and neoadjuvant chemotherapy, surgery, and myeloablative treatment followed by autologous stem cell transplant for high-risk disease. Radiation is not standard treatment, but may be offered to palliate symptoms for low- and moderate-risk disease.

### GANGLIONEUROMA

This tumor of neural crest origin is composed of mature ganglion cells that are well-differentiated and benign. The most common location is in the sympathetic ganglia of the posterior mediastinum. It is a disease of older children and young adults. Treatment is surgical and is expected to be curative.

### PARAGANGLIOMA

Tumors of the paraganglia are extraadrenal pheochromocytomas, and may occur in the posterior mediastinum. They are rare, usually benign, solitary, and may be associated with multiple endocrine neoplasia. Not all paragangliomas are functional, but those that are secrete catecholamines that cause the clinical syndrome of episodic hypertension, palpitations, sweating, and severe headache. Levels of serum or urine catecholamine metabolites are usually elevated. The majority of these masses are apparent on CT scanning, and appear vascular if intravenous contrast is given. Tumor invasion of adjacent structures suggests malignancy. Complete surgical resection is the treatment, and may be done with a minimally invasive approach. Because of the vascular nature of these tumors, intraoperative bleeding may be significant. Patients with functional tumors should receive α- and β-blocking agents preoperatively in the same manner as adrenal pheochromocytoma patients do.

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## MEDIASTINAL DISEASE BOARD REVIEW QUESTIONS (CHAPTER 17)

1. Which of the following is true regarding thymomas?
   A. Thymoma classification is based on tumor size.
   B. The presence of myasthenia gravis is a risk factor for poor outcome.
   C. Neoadjuvant therapy can be used for large malignant tumors.
   D. Debulking operations are a mainstay of thymoma treatment.
   E. Fine-needle aspiration is the preferred method of diagnosis.

2. Which of the following is true concerning mediastinal anatomy?
   A. The junction of the superior vena cava and the right atrium is located in the anterior-superior mediastinum.
   B. The mediastinal space arises from a combination of the ventral and dorsal esophageal mesenteries.
   C. Neurogenic tumors commonly occur in the middle mediastinum.
   D. The lungs and pericardium arise from the dorsal mesoesophagus.
   E. Bronchogenic cysts are the result of aberrant budding from the dorsal foregut.

3. Which is true regarding neurogenic tumors of the mediastinum?
   A. The peak incidence of neuroblastoma is in early adulthood.
   B. Extraadrenal neuroblastomas are typically aggressive.
   C. Surgical resection of a neuroblastoma is usually not curative.
   D. The posterior mediastinum is the most common location for neuroblastoma.
   E. Paragangliomas are, by definition, nonfunctional tumors.

4. Which of the following is true regarding germ cell tumors?
   A. The mediastinum is the most common site of primary germ cell tumors.
   B. Nonseminomatous tumors are associated with Klinefelter's syndrome.
   C. Surgical removal of residual disease in nonseminomas is not indicated after chemotherapy.
   D. Malignant seminomas are highly resistant to treatment.
   E. Serial β-hCG and AFP levels are not useful after initial therapy.

5. Which of the following is correct?
   A. Prophylactic antibiotics are contraindicated in spontaneous pneumomediastinum.
   B. Treatment of acute mediastinitis is primarily medical, with surgery reserved for failure of medical therapy.
   C. Corticosteroid therapy has been shown to be highly effective for sclerosing mediastinitis.
   D. Anticoagulation after thrombolysis and aspirin after stent placement are recommended treatment guidelines for vena caval thrombosis.
   E. The majority of patients with superior vena cava syndrome have an underlying benign process.

## ANSWERS

1. **Answer: C.** Neoadjuvant chemotherapy is recommended for large malignant thymomas. Thymoma classification is based on histologic examination of the capsule and invasion. The presence of myasthenia gravis is not a risk factor for poor outcome. Debulking operations do not provide significant benefit in the absence of complete resection. Fine-needle aspiration is controversial and may fail to distinguish a thymoma from a lymphoma.
2. **Answer: B.** The mediastinal space arises from the ventral and dorsal esophageal mesenteries. The junction of the SVC and right atrium is located in the middle mediastinum. Neurogenic tumors most commonly occur in the posterior mediastinum. The lungs and pericardium arise from the ventral mesoesophagus. Bronchogenic cysts are the result of aberrant budding from the ventral foregut.
3. **Answer: D.** The posterior mediastinum is the most common location for neuroblastoma. The peak incidence of neuroblastoma is in infancy and early childhood. Extraadrenal neuroblastomas are typically less aggressive and surgical resection is usually curative. Some paragangliomas can secrete catecholamines.
4. **Answer: B.** Nonseminomatous tumors are associated with Klinefelter's syndrome. The mediastinum is the most common site of metastatic germ cell tumors. Serial β-hCG and AFP levels are useful after initial therapy, particularly for nonseminomatous tumors, and surgical removal of residual disease in nonseminomas is indicated if levels remain elevated. Malignant seminomas are highly responsive to treatment.
5. **Answer: D.** Anticoagulation after thrombolysis and aspirin after stent placement are recommended treatment guidelines for vena caval thrombosis. Prophylactic antibiotics are indicated in the initial treatment of spontaneous pneumomediastinum. Treatment of acute mediastinitis is primarily surgical. Corticosteroids have variable efficacy in sclerosing mediastinitis. The majority of patients with SVC syndrome have an underlying malignant process.

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# 18 Chest Wall Tumors

*Robert A. Meguid*
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**KEY CONCEPTS**

- Epidemiology
  - Chest wall tumors constitute 5 percent of thoracic tumors and less than 1 percent of all primary tumors; between 40 and 60 percent are malignant. Tumors may originate primarily in the chest wall, may metastasize to it, or extend into it via local invasion from adjacent structures. Morbidity and mortality are specific to the particular tumor type.
- Clinical features
  - Chest wall tumors often present as painless enlarging masses, with pain developing with progressive growth. Constitutional symptoms may also develop.
- Diagnosis
  - After initial history and physical examination, radiographic imaging can reveal anatomic location, tissue of origin, involvement or invasion of adjacent structures, and ultimately the response to therapy or recurrence. Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-CT (PET-CT) are useful, dependent on the tissue type and location. Needle, incisional, or excisional biopsy is usually necessary to determine tissue type and aids in further management.
- Treatment
  - Multidisciplinary management is helpful given the rarity and diverse nature of chest wall tumors. Medical treatment varies with different tumor types. Chemotherapy and radiation therapy may be used.
  - Surgical treatment varies with different tumors types. In general, malignant tumors should be resected to negative margins including the uninvolved rib above and below the tumor. Chest wall reconstruction is necessary for defects greater than 5 cm and those resulting in exposure of vulnerable underlying structures, and aims at stabilizing the chest wall during respiration and excursion.
- Outcome/prognosis
  - Outcomes of the treatment are tumor-dependent. Long-term surveillance is accomplished with serial examination and imaging.

## INTRODUCTION

Tumors involving the chest wall are uncommon, constituting 5 percent of all thoracic masses and less than 1 percent of all primary tumors.[1] Tumors may originate primarily in the chest wall, may metastasize to it, or extend into it via local invasion from adjacent structures. As a group, chest wall tumors can be organized by their tissue of origin or occurrence and further divided into malignant and benign tumors. Chest wall tumors are listed in Table 18-1. In characterizing these tumors, we have identified them based on the tissue of origin in the chest wall, moving from the parietal pleura through the chest outward to the skin.

Malignant and benign primary chest wall tumors are roughly equally distributed with malignant lesions representing 40 to 60 percent of all chest wall tumors.[1,2] Of primary malignant chest wall tumors, chondrosarcomas occur with the most frequency, constituting approximately 35 percent.[3] Presenting with decreasing frequency are solitary myelomas (plasmacytomas) (25 percent), Ewing sarcomas (15 percent), osteosarcomas (15 percent), and lymphomas (10 percent).

The most common benign tumor of the chest wall is fibrous dysplasia, accounting for approximately 40 percent of cases. Chondromas are also common, constituting 30 percent of cases. Other, less frequently occurring benign chest wall tumors include osteochondromas, lipomas, desmoid tumors, neurofibromas, and giant cell tumors.

Metastases more commonly seen involving the chest wall include melanoma, breast carcinoma, lung carcinoma, renal cell carcinoma, and mesothelioma. Details of each tumor type and specific management strategies are discussed at the end of this chapter.

**TABLE 18-1: Chest Wall Tumor Types by Tissue of Origin**

| Tissue of Origin | Benign | Malignant |
|---|---|---|
| **Soft-tissue tumors** | | |
| Parietal pleura | Benign localized solitary fibrous tumor | Malignant localized solitary fibrous tumor<br>Mesothelioma |
| Bone, cartilage, and connective tissue | Fibrous dysplasia<br>Chondroma<br>Osteochondroma<br>Chondromyxoid fibroma<br>Langerhans cell histiocytosis<br>Aneruysmal bone cyst<br>Ossifying fibromyxoid tumor<br>Giant cell tumors | Chondrosarcoma<br>Osteosarcoma<br>Ewing sarcoma and primitive neuroectodermal tumor<br>Primary pleuropulmonary synovial sarcoma<br>Adamantinoma |
| Muscle | Leiomyoma<br>Rhabdomyoma | Leiomyosarcoma<br>Rhabdomyosarcoma |
| Nerve | Neurofibroma<br>Schwannoma (benign peripheral nerve sheath tumor)<br>Paraganglioma<br>Ganglioneuroma | Neurofibrosarcoma<br>Malignant peripheral nerve sheath tumor (malignant schwannoma)<br>Ganglioneuroblastoma<br>Neuroblastoma |
| Lymphovascular | Cavernous hemangioma<br>Glomus tumor<br>Lymphangioma | Angiosarcoma |
| Soft tissue | Desmoid tumor<br>Lipoma<br>Spindle cell lipoma<br>Elastofibroma<br>Other benign soft-tissue tumors<br>Cutaneous nevus | Malignant fibrous histiocytoma<br>Liposarcoma<br>Soft-tissue sarcoma<br>Proximal-type epithelioid sarcoma<br>Radiation-induced sarcoma<br>Skin cancer |
| Hematologic | | Lymphoma (primary)<br>Myeloma (plasmacytoma) |
| Common metastases to or invasion into chest wall | | Lung cancer<br>Breast cancer<br>Melanoma<br>Mesothelioma<br>Lymphoma (metastatic)<br>Renal cell carcinoma |

Infectious etiology is also possible, with primary pulmonary infections sometimes invading into the chest wall. These are most commonly due to fungal diseases, such as nocardia and actinomyces. Discussion of these infections is outside the scope of this chapter.

The clinical presentation of chest wall tumors varies from an incidentally found asymptomatic mass to a painful visible lesion. Initially, often chest wall tumors are asymptomatic, but as they continue to grow and invade the chest wall, pain is almost inevitable especially in malignant lesions. Workup begins with a history and physical examination, and includes axial imaging and often biopsy to establish tissue diagnosis. Management of rarely encountered tumors is aided by a multidisciplinary oncologic approach.

The aims of chest wall tumor resection are to achieve cure or control of the disease and to leave the chest wall stable enabling the patient to engage in the normal physiology of respiration, with a good quality of life. Management of chest wall tumors often poses the surgical challenge of resection, followed by closure or reconstruction of defects greater than 5 cm or involving two or more ribs. Reconstruction of the latter can be aided through the employment of composite prosthetic materials and techniques of rotational, advancement and free flaps with the assistance of surgeons trained in plastic reconstructive techniques.

## CLINICAL FEATURES

The presentation of chest wall tumors ranges from incidentally discovered painless lesions to painful enlarging masses. They are asymptomatic in 20 percent of patients, and local trauma is frequently the inciting event drawing attention to the presence of a lesion. The remaining 80 percent of patients present with

enlarging masses, local or adjacent pain, dyspnea, cough, and symptoms of neurologic or vascular involvement.[4] As these lesions involve a dynamic structure of the chest wall, patients may complain of exertion-related pain. Patients may also experience nonspecific symptoms including fatigue, muscle aches, night sweats, and weight loss. Painful chest wall masses are more likely to be malignant in nature due to more rapid growth of the former, as well as invasion into adjacent structures, rather than displacement of them.

## DIAGNOSIS

Suspicion of the presence of a chest wall tumor begins with obtaining a history and performing a physical examination of the patient. Patients may describe a history of chest or shoulder pain, dyspnea, new-onset cough, constitutional symptoms, swelling of the neck or head, ipsilateral ptosis, myosis, anhidrosis, and enophthalmos (Horner syndrome). History may also reveal prior malignancy.

Additional history should include temporal onset of the lesion, associated symptoms such as the quality and nature of the pain, presence of radiating pain, history of environmental exposures, such as asbestos or radiation, and history of constitutional symptoms including weight loss, change in appetite, dyspnea with or without exertion, fevers, chills, and night sweats.

Physical examination is focused on the area of interest, but it should also include examination for regional adenopathy, neural involvement, and musculoskeletal deficits. This includes location, size, appearance, and quality on palpation of the lesion, presence of any satellite lesions, ulcerations, or sinuses. Neurologic involvement may include nerves of the brachial plexus, the long thoracic nerve (with resulting winged scapula), or the sympathetic chain (with resulting Horner syndrome as already described). Auscultation of the chest may reveal diminished breath sounds or the presence of a rub associated with an effusion.

Although chest wall tumors are rare and varied, a combination of clinical information with appropriate imaging can suggest a specific diagnosis. Imaging can reveal anatomic location, tissue of origin, involvement or invasion of adjacent structures, and ultimately response to therapy or recurrence.

Following the history and physical examination, our workup algorithm proceeds to chest radiograph and computed tomography (CT), with the selective use of magnetic resonance imaging (MRI) for soft-tissue masses and concern for vascular or neurologic involvement by the tumor. The use of positron emission tomography-CT (PET-CT) is becoming more widespread in diagnosis of malignancies. We have included optimal modalities of imaging and characteristic radiographic findings of different chest wall tumors with the descriptions of each tumor type at the end of this chapter. In general, slow-growing, benign tumors displace adjacent tissues, with maintenance of well-defined tissue planes. More aggressive malignant tumors tend to invade adjacent tissues.

Chest radiography is commonly the first imaging modality performed in diagnosis and evaluation of patients with chest wall tumors, and is often performed prior to referral for evaluation by the thoracic surgeon. It may help characterize chest wall or pulmonary lesions, and may also identify incidental lesions. Although the value of the chest radiography in diagnosis and operative planning is limited, it may help characterize the location, size, and nature of the lesion, involvement of bony versus soft tissue, and presence of ossification or calcification. It also can be useful for following the growth of a chest wall lesion.[5] The use of ultrasound to define borders of tumors has been described but this is not our preferred modality.[6]

CT is useful in determining the location and size of the lesion as well as providing information on presence, and extent, of invasion of adjacent structures. It is more accurate than chest radiography in the assessment of tumor morphology. Additional techniques to elucidate tumors in the plane of the ribs include off-axial imaging with an angled gantry, or the use of thin-sectioning with breath-holding.[5] A contrast CT can provide information on the vascularity of a tumor, and help differentiate tissue planes and types.

The use of MRI for characterizing chest wall tumors is increasing. MRI has the ability to provide distinction of anatomic involvement, revealing subtle tissue planes, and can differentiate between tumor and adjacent inflammation. Information on invasion or encasement of vascular and neurologic structures, as well as characterization of the nature of the lesion, can be determined. It is specifically useful for characterization of soft-tissue masses. The use of cardiac gating and respiratory compensation can improve image resolution by minimizing motion artifact associated with respiratory excursion of the chest wall. Additional techniques include prone positioning of patients.[5] Due to these advantages, MRI is our preferred modality for evaluating chest wall tumors.

PET-CT is a useful adjunct for evaluating metabolic activity, especially in the setting of metastatic malignancies, and to assess lymph node involvement. It can also be used to stage soft-tissue sarcomas. In the setting of benign and slow-growing tumors, the degree of $^{18}$F-fluoro-2-deoxy-D-glucose (FDG) uptake may be mild as compared with faster-growing tumors. These data may aid in differentiating between tumor types and can assist in both the diagnosis as well as tumor staging.[7,8]

PET-CT is 96 percent accurate in the diagnosis of T-stage, N-stage, and M-stage of patients with bone and soft-tissue sarcomas. Accuracy of diagnosis of T-stage is increased to 99 percent using a combination of PET-CT, CT, MRI, Technetium-99m-hydroxymethylene diphosphonate bone scintigraphy, and plain radiography studies. Accuracy of diagnosis of N-stage and M-stage is increased to 97 percent using a combination of PET-CT with the other imaging modalities. PET scanning without the combination of CT imaging is accurate only in 80 percent of T-staging, 93 percent of N-staging, and 91 percent of M-staging of patients with bone and soft-tissue sarcomas. The overall accuracy

in diagnosis of PET-CT combined with other imaging modalities was 87 percent in the patients with bone and soft-tissue sarcomas.[8] Therefore, we use the combined modality PET-CT to aid in staging of bone and soft-tissue sarcomas.

Tissue diagnosis, in conjunction with staging, guides management of chest wall tumors. Diagnosis of smaller tumors, generally less than 5 cm in diameter, is confirmed by excisional biopsy with 1- to 2-cm margins. For larger lesions, and in tumors with involvement of adjacent structures, incisional biopsy is used. Principles for soft-tissue sarcomas apply in regards to positioning and orientation of the initial incision so that it may be included with the tumor specimen, should re-excision be necessary. Fine-needle aspiration can help in the diagnosis of some chest wall tumors, as noted later in the chapter, but is not reliably useful for determination of malignant potential and tumor grade of soft-tissue masses. Although core-needle biopsy can provide insight into tumor architecture, it is our experience that to obtain enough tissue to provide an accurate diagnosis and stage, which may require immunohistochemical staining in addition to histologic examination, excisional and incisional biopsies are preferable.

## STAGING AND PREOPERATIVE TESTING

There is currently no uniform staging system for all primary tumors occurring in the chest wall. The staging of chest wall tumors is based on the staging classification of the primary tumor type involved. Staging workup, therefore, is diagnosis-specific, and may entail additional imaging studies (CT or ultrasound of the abdomen, CT or MRI of the head), invasive studies (bronchoscopy, esophagoscopy, colonoscopy), and laboratory evaluation to rule out nodal and metastatic diseases.

Preoperative pulmonary function tests are routinely obtained, in this event, pulmonary resection is necessary to achieve tumor-free margins with en bloc resection. In addition, routine preoperative workup is performed to rule out comorbidities that may compromise a patient's ability to tolerate treatment or posttherapeutic outcome.

## MANAGEMENT

We favor a multidisciplinary approach to the management of malignant, complicated, and rare chest wall tumors. Regular review of patients with chest wall tumors at institutional tumor boards facilitates diagnosis and management, drawing on the experience of pathologists, radiologists, medical oncologists, radiation oncologists, and surgical oncologists. This is critical when considering the rare nature of chest wall tumors, given the overall scarcity of retrospective experience and prospective data on their management. We also find that it aids in the identification of patients who will most likely benefit from neoadjuvant and adjuvant chemotherapy and radiation therapy.

## INDICATIONS FOR RESECTION

Surgical management remains the mainstay of therapy for chest wall tumors. This is in part, to cure benign and limited malignant lesions, and in part, to aid in diagnosis and guide additional therapy. Specific recommendations for the management of different chest wall tumors are outlined later, accompanying the review of each tumor type.

Surgical therapy of malignant lesions typically necessitates wide local excision with confirmation of histologically negative tissue margins. In general, full-thickness resection, including skin, if involved, is performed. Resection often includes ribs and soft tissues from the interspace above and below the lesion. In the case of local invasion into adjacent tissues, including lung, heart, liver, kidney, spleen, diaphragm, and major neural and vascular structures, resection is indicated where possible, but involvement of "vital structures" may limit the ability to achieve tumor-free margins. Adhesions between chest wall and lung parenchyma are resected en bloc with the tumor, with preservation of as much adjacent lung parenchyma as possible while still achieving an adequate tumor-free margin. Therefore, the judgment of the surgeon is critical in the complex management of chest wall tumors.

## NONSURGICAL MANAGEMENT

Although the mainstay of curative therapy for chest wall tumors is margin-negative surgical resection, specific tumor types are treated primarily with chemotherapy and radiotherapy, and chest wall tumors presenting in advanced local stage are frequently treated with either adjuvant or even neoadjuvant therapy.

In addition, evidence of extension of disease into adjacent organs or cavities, or presence of metastases, may prohibit safe surgical resection or prevent it from achieving control of symptoms or cure. Consideration of the utility of surgery is especially critical for several circumstances, including patients with a large-tumor burden when it is unclear if the patient will tolerate the extent of resection such as pulmonary invasion necessitating large or bilateral lung resections, patients with distant metastases, or patients who are severely malnourished.

## CHEST WALL RECONSTRUCTION

The goal of reconstruction is to recreate a stable, nonparadoxically functioning chest wall, which will afford the patient minimal additional work to engage in efficient respiration, as well as efficient and comfortable excursion during activity. Reconstruction beyond primary tissue coverage is usually not necessary for defects involving a single rib, less than 5 cm in diameter, lying beneath the scapula or occurring posteriorly on the rib cage. However, following resection of anterior and lateral lesions with resulting chest wall

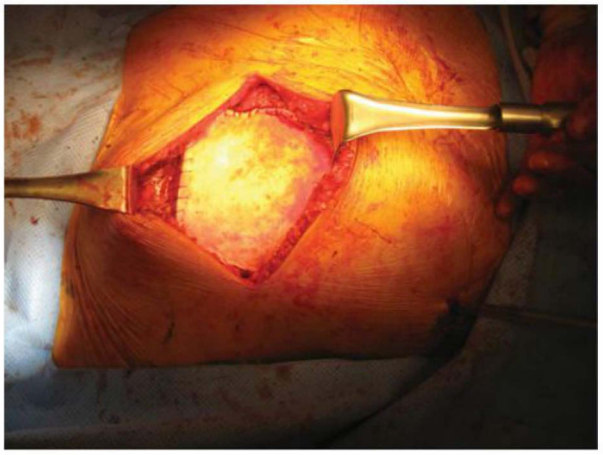


**FIGURE 18-1** Photograph of the reconstructed chest wall following resection of an 11.4-cm grade I chondrosarcoma with resection of medial aspects of the fourth through sixth ribs. Reconstruction was performed with 2 mm Gore Tex sutured to the borders of the defect. (Image courtesy of Douglas Wood, MD.)



**FIGURE 18-2** Reconstruction of the chest wall in a patient undergoing resection of recurrent chest wall sarcoma on the right chest. Right chest wall following initial resection and recurrence of tumor, with intraoperative planning and marking of landmarks. (Image courtesy Dan Suver, MD.)

defects greater than 5 cm in diameter, chest wall reconstruction should be performed. This also applies to defects resulting from the resection of two or more adjacent ribs, which can lead to chest wall instability. In addition, vulnerability of underlying structures should be considered. Specifically, sternal resections and those leading to exposure of the heart and great vessels should be reconstructed.

The chest wall is a dynamic structure with complex three-dimensional movement with respiration. Reconstruction using rigid material can lead to paradoxical movement. To maintain physiologic respiratory movement following chest wall reconstruction, nonelastic, pliable, permanent material such as polypropylene mesh (Marlex, Chevron Phillips Chemical Company LLC, The Woodlands, Texas, USA) or Gore Tex (W. L. Gore & Associates, Inc., Newark, Delaware, USA), with the advantage of being fluid impermeable, can be affixed to the ribs to fill defects (Fig. 18-1).[6] In addition, ribs can be replicated using metal plates anchored to the existing rib margins (Strasbourg Thoracic Osteosyntheses System—STRATOS™; MedXpert GmbH, Heitersheim, Germany), with polypropylene mesh affixed to them using nonabsorbable suture material, and the reconstructed chest wall covered with myocutaneous or muscle rotational flap. It is important to return the patient to a neutral position on the operating table during reconstruction, so that the mesh is not secured with the rib spaces expanded.

More rigid chest wall reconstruction can be achieved with methyl methacrylate sandwiched between two pieces of nonabsorbable mesh (Figs. 18-2, 18-3, 18-4, and 18-5). Reconstruction of a resected sternum may be accomplished with this polypropylene mesh–methyl methacrylate sandwich or with polypropylene reinforced with omentum.[9,10] This is useful when the heart or great vessels are exposed following medial costal or sternal resection. The use of steel wire mesh as a foundation for reconstructing large defects has been described in the past, but we do not favor its use.[11,12]

It is important to consider the location of the reconstruction relative to more dynamic areas of the chest wall. For example, posterior resections may allow the tip of the scapula to hang up on resected or adjacent ribs. In this instance, posterior reconstruction is necessary to preserve function of mobility of the arm and the scapula. Another example is in the inferior costal border. Here, we have found that rigid prostheses may be poorly tolerated when patients bend over onto them, and preferentially use Gore Tex or a flexible mesh.



**FIGURE 18-3** Reconstruction of the chest wall in a patient undergoing resection of recurrent chest wall sarcoma on the right chest. Reconstruction of resulting chest wall defect with polypropylene mesh-methyl methacrylate sandwich. (Image courtesy Dan Suver, MD.)

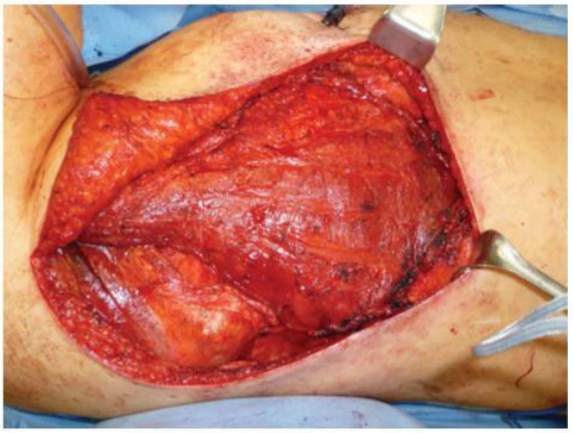


**FIGURE 18-4** Reconstruction of the chest wall in a patient undergoing resection of recurrent chest wall sarcoma on the right chest. Latissimus dorsi muscle flap overlying chest wall reconstruction. (Image courtesy Dan Suver, MD.)

The use of tissue transfer techniques, such as advancement skin flaps, skin grafting, rotational muscle flaps, and myocutaneous flaps, may aid in closure or coverage of large soft-tissue defects, especially when skin is involved, or in irradiated tissue beds. Based on location and extent of resection, useful muscle flaps include the pectoralis major, latissimus dorsi, and rectus abdominus (Figs. 18-6, 18-7, 18-8, and 18-9). We prefer to enlist the help of an experienced plastic reconstructive surgeon for large, complex repairs.

Reoperation for recurrences of chest wall tumors, following initial resection and reconstruction, poses a particular challenge. Not only must the further loss of chest wall tissue be managed, but also the adhesion between reconstructive prostheses and adjacent structures. Therefore, great care must be taken during dissection.



**FIGURE 18-5** Reconstruction of the chest wall in a patient undergoing resection of recurrent chest wall sarcoma on the right chest. Split-thickness skin graft overlying muscle flap. (Image courtesy Dan Suver, MD.)

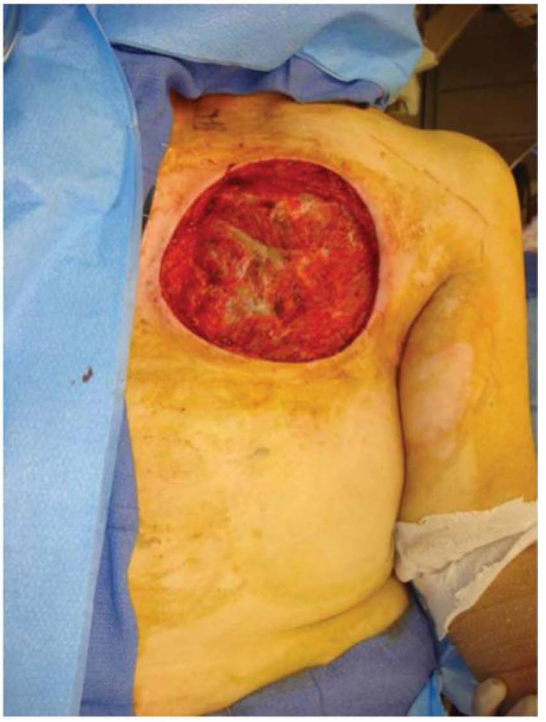


**FIGURE 18-6** Resection of recurrent chest wall sarcoma and reconstruction of anterior chest wall using a latissimus dorsi myocutaneous flap: resulting defect prior to reconstruction. (Image courtesy of Merhan Habibi, MD.)



**FIGURE 18-7** Resection of recurrent chest wall sarcoma and reconstruction of anterior chest wall using a latissimus dorsi myocutaneous flap: planning flap procurement. (Image courtesy of Merhan Habibi, MD.)

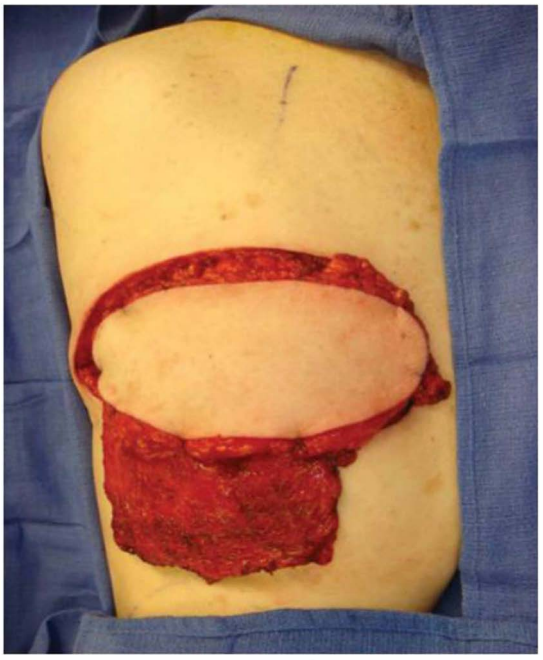


**FIGURE 18-8** Resection of recurrent chest wall sarcoma and reconstruction of anterior chest wall using a latissimus dorsi myocutaneous flap: preparation of latissimus dorsi myocutaneous flap. (Image courtesy of Merhan Habibi, MD.)

We have encountered various complications associated with chest wall reconstruction, including generalized inflammation, seroma formation, herniation of pneumatoceles, development of pleuroparenchymal fistulae, infection of the surgical site and prostheses, persistent drainage from sinuses associated with prostheses, and presence of enlarged lymph nodes that may be inflammatory or indicative of cancer recurrence.

Management of these can be challenging for the surgeon as well as the patient. In the setting of cancer cachexia, patients may not tolerate indolent complications or complex operations to treat them.

## SURVEILLANCE

Most primary chest wall tumors recur locally. Some also metastasize to the lungs, liver, or elsewhere, as described later. Long-term surveillance is achieved by serial examination of the patient and axial imaging. We generally see patients 2 to 4 weeks after the surgery, followed by clinic visits at 4- to 6-month intervals for 2 years, and then yearly for an additional 8 years, with a noncontrast chest CT obtained annually for 10 years. We engage in more frequent observation for aggressive tumors, and longer surveillance for more indolent tumors.

## TUMORS OF THE CHEST WALL

### Parietal Pleura

#### BENIGN

***Benign Localized Solitary Fibrous Tumor.*** Solitary fibrous tumors are spindle cell neoplasms, commonly of pleural origin, and lacking epithelial differentiation. Thoracic solitary fibrous tumors constitute two-thirds of solitary fibrous tumors, the remainder being extrathoracic in location.[13] Between one-quarter and one-third occur in the parietal pleura of the chest wall, diaphragm, or mediastinum, while the majority occur in the visceral pleura (Figs. 18-10, 18-11, 18-12, and 18-13).[14,15] Solitary fibrous tumors of the pleura are characterized by combinations of cellular, fibrous, and

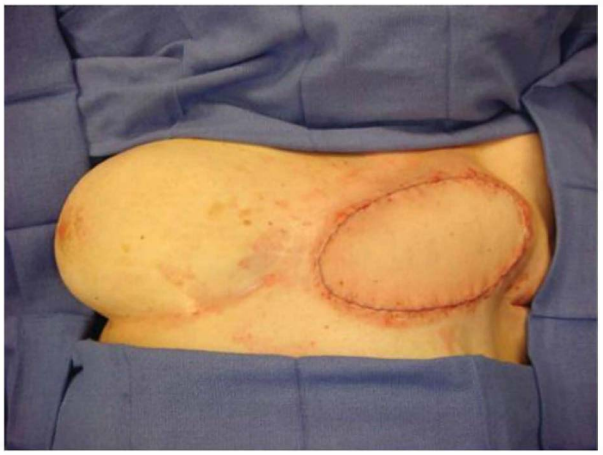


**FIGURE 18-9** Resection of recurrent chest wall sarcoma and reconstruction of anterior chest wall using a latissimus dorsi myocutaneous flap: following reconstruction with flap. (Image courtesy of Merhan Habibi, MD.)

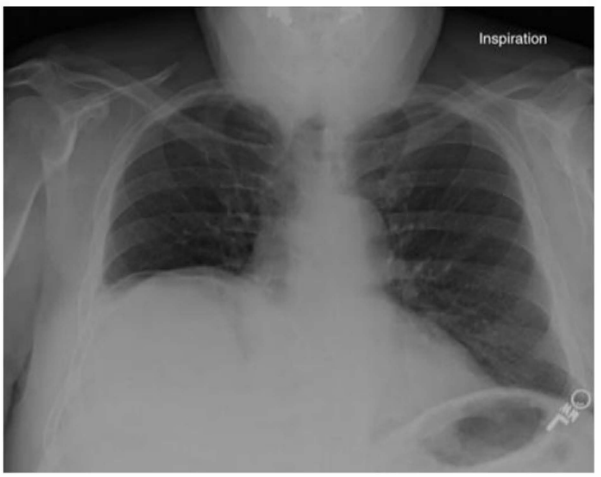



**FIGURE 18-10** PA chest radiograph of a 68-year-old man with a large right chest mass. Subsequent biopsy determined this to be a solitary fibrous tumor. (Image courtesy Douglas Wood, MD.)




**FIGURE 18-11** Lateral chest radiograph of a 68-year-old man with a large right chest mass. Subsequent biopsy determined this to be a solitary fibrous tumor. (Image courtesy Douglas Wood, MD.)

hemangiopericytomatous components, with fibrotic, thickened investing pleura.

Localized solitary fibrous tumors of the pleura occur equally in men and women, in all age groups but with preponderance to presentation in the sixth and seventh decades

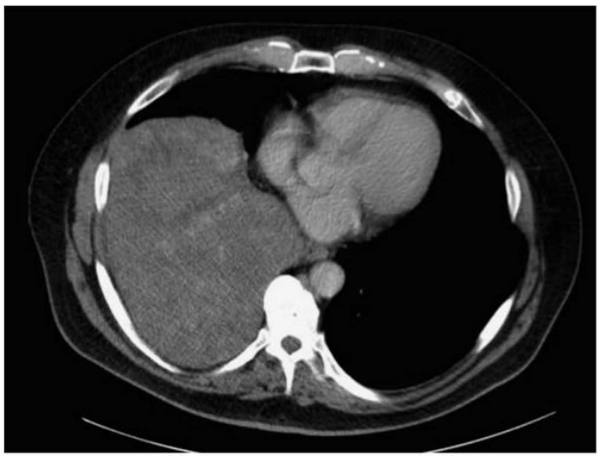


**FIGURE 18-12** Abdominal CT image of a 68-year-old man with a large right chest mass. This image demonstrates the size and location of the chest wall solitary fibrous tumor. Extirpation of the tumor required resection of adjacent lung parenchyma as well as diaphragm and a wedge of the right lobe of the liver, into which there was superficial invasion. (Image courtesy of Douglas Wood, MD.)

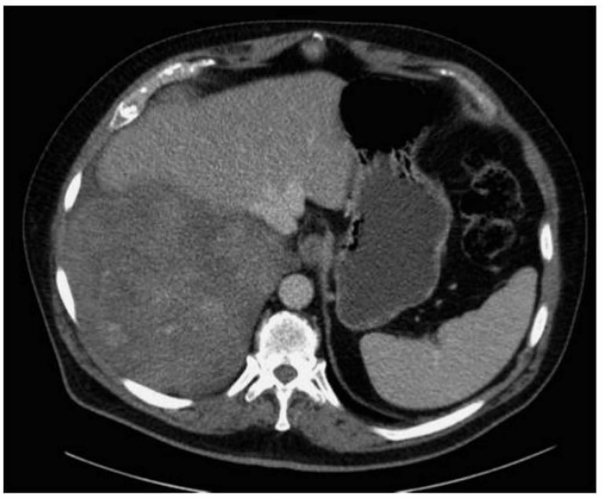


**FIGURE 18-13** Abdominal CT image of a 68-year-old man with a large right chest mass. This image demonstrates the size and location of the chest wall solitary fibrous tumor, with involvement of the liver. Extirpation of the tumor required resection of adjacent lung parenchyma as well as diaphragm and a wedge of the right lobe of the liver, into which there was superficial invasion. (Image courtesy of Douglas Wood, MD.)

of life. Patients with localized fibrous pleural tumors most commonly present with ipsilateral chest pain, dyspnea, and cough. They may rarely have ipsilateral pleural effusions, or vena cava compression with associated symptoms. Approximately one-quarter of patients are asymptomatic at diagnosis. On chest radiography, tumors may be evident as sharply circumscribed masses in the periphery of the lung fields, with homogeneous appearance on chest CT.[14] Following tissue diagnosis via core-needle biopsy or incisional biopsy, treatment is complete resection, which is usually curative.

## MALIGNANT

***Malignant Localized Solitary Fibrous Tumor.*** Malignant localized solitary fibrous tumors of the pleura are a subgroup of localized solitary fibrous tumors of the pleura, and for the most part share histologic features, presentation, and workup, with their benign counterparts, except as noted later. Localized solitary fibrous tumors of the pleura demonstrate malignant behavior in 10 to 36 percent of cases, with malignancy associated with larger tumors, tumors with increased cellularity, and nonpedunculated tumors, emphasizing the importance of adequate tissue sampling in cases of tumors with mixed components.[14]

Their presentation is also comparable with that of benign localized solitary fibrous tumors of the pleura. However, the presence of an ipsilateral pleural effusion is associated with approximately one-third of malignant localized solitary fibrous tumors of the pleura, which is significantly greater than that in their benign counterparts.[14]

Approximately half of all malignant localized solitary fibrous tumors of the pleura recur, with a single site of recurrence in three-quarters of patients. Two-thirds of recurrent localized solitary fibrous tumors originate from the parietal pleura.[14] The disease-free interval varies widely, between 6 months and 13 years following surgical resection.[15] Metastatic disease is treated with palliative chemotherapy, including doxorubicin and ifosfamide.[13]

### MESOTHELIOMA

Mesotheliomas are diffuse malignant tumors of the pleura, with epithelial differentiation. These are addressed in-depth in a separate chapter.

## BONE AND CARTILAGE

### Benign

#### FIBROUS DYSPLASIA

The majority of benign chest wall lesions are due to fibrous dysplasia of the bone, accounting for approximately 40 percent of benign chest wall lesions. These most commonly present in the third and fourth decades of life, with an equal distribution between men and women. In children, they are the most common benign lesion of the ribs.

Fibrous dysplasia is the result of failure of differentiation of mesenchymal osteoblasts. Presenting findings commonly include pain due to pathologic fracture or bone deformity. On CT imaging, fibrous dysplasia has an amorphous calcified appearance. On both T1- and T2-weighted MR imaging, they have heterogeneous signal intensity.[5] Treatment is surgical excision to both relieve symptoms and rule out malignant disease.

#### CHONDROMA

Similar to fibrous dysplasia of bone, chondromas are the most common benign tumor of cartilage. They account for between 10 and 30 percent of benign chest wall lesions.[3,16] These most commonly present in the second and third decades of life, with an equal distribution between men and women. Their appearance on radiographic studies is similar to that of malignant chondrosarcomas. As a result, surgical biopsy, and often resection, is necessary to rule out malignancy and treat symptomatic lesions.

#### OSTEOCHONDROMA

Osteochondromas generally present in adulthood. Patients typically present with masses associated with fractures or rib deformities. On imaging, they appear as masses with eccentric growth patterns at the costochondral junction. CT imaging of osteochondromas is characterized by a cartilaginous mass with a calcified cap. On T2-weighted MRI, osteochondromas have a high signal intensity.[5] Osteochondromas can undergo malignant transformation, but most complications are associated with a mass effect and displacement of adjacent structures. Malignant lesions may have an irregular appearance on imaging. Surgical resection is necessary to rule out malignancy and to treat symptomatic lesions.

#### CHONDROMYXOID FIBROMA

Chondromyxoid fibromas are tumors consisting of chondroid, myxomatous, and fibrous components. Occurring in long bones around the knee in approximately half of all cases, these rarely occur in bones of the chest wall. When occurring in the chest, they typically present in early adulthood, with equal distribution between men and women, and have been reported to occur in the rib, spine, scapula, and sternum.[17] They are usually lobular with sclerotic bands of tissue-separating lobules.

Chondromyxoid fibromas appear on radiographs as well as demarcated masses with scalloped sclerotic borders, lacking internal calcification. On CT imaging, they characteristically appear as an expansile mass with diffuse or heterogeneous enhancement, bone destruction, lobulated margins with septations, and a sclerotic rim. On T2-weighted MRI, they have high signal intensity.[5] Treatment is surgical resection, in part to rule out malignant disease.

#### LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis, or dendritic cell histiocytosis (also previously known as histiocytosis X), is a rare disease resulting from clonal proliferation of dendritic Langerhans cells. It may present as unifocal, multifocal unisystem, or multifocal multisystem disease. Affecting children, with a peak incidence between 5 and 10 years of age, unifocal disease carries a favorable prognosis.[18] Langerhans cell histiocytosis most commonly presents in the skull and long bones of the upper extremity, but has been reported to occur in ribs.[19] Lesions present as painful bone swelling. Histologic diagnosis is made by identification of Langerhans cells, and can be confirmed by demonstration of characteristic Birbeck granules on electron microscopy. Treatment is surgical resection, in part to rule out malignant disease, or radiation therapy if the diagnosis has been confirmed. Systemic disease is treated with chemotherapy.

#### ANERUYSMAL BONE CYST

Aneruysmal bone cysts are blood-filled cysts that may develop rapidly and typically present in early adulthood. They are characterized by a network of blood-filled cysts lined with fibroblasts and multinucleated giant cell osteoclasts. In the chest, these commonly develop in the posterior elements of the spine, but may occur in the ribs or clavicles.

On axial imaging, they characteristically appear as expansile masses with cortical thinning and well-defined

inner margins. On both T1- and T2-weighted MRI, they have a heterogeneous signal, with fluid–fluid levels, and may appear septated.[5] Fluid–fluid levels are the appearance of two different density fluids, usually water-density fluid layering over blood. Surgical resection is indicated for symptomatic lesions.

### OSSIFYING FIBROMYXOID TUMOR

Ossifying fibromyxoid tumors are composed of chords or nests of small, round cells, with a hyaline fibrosis-like myxoid matrix, usually surrounded by an incomplete bone shell. They typically present in adulthood, with a median age of 50 years, occurring with a 2:1 male-to-female ratio. Approximately 15 percent occur in the chest wall, most frequently involving the ribs.[20]

Patients present with a slow-growing, nontender mass, progressing over several years. On CT imaging, they characteristically appear as a vascularized, bubble-shaped, intracortical, osteolytic lesion surrounded by a sclerotic band of tissue with confluent contours. They are contrast enhancing, and on T2-weighted MRI, they have high signal intensity.[5] Treatment is wide resection, as recurrence is reported in a quarter of all patients treated with local excision.[20]

### GIANT CELL TUMORS

Giant cell tumors are benign tumors arising from the metaphyses and epiphyses of bones, accounting for approximately 5 percent of primary bone tumors.[21] Although approximately 80 percent arise from long bones, with 55 percent occurring in the lower extremities, they occasionally arise from the epiphysis of the head or tubercle of ribs.[22–28] Giant cell tumors most commonly present in the third and fourth decades of life, but can present in children, with a slight increase in incidence in females, and may be mistaken for giant cell reparative granulomas, brown tumors of hyperparathyroidism, aneurismal bone cysts, or fibrous dysplasia. Giant cell tumors exist in a spectrum of patterns, and the aggressive variant is associated with invasion of surrounding soft tissues. Patients may present with lytic lesions encompassing the adjacent bone, and approximately 20 percent have an overlying soft-tissue mass on presentation.

CT imaging may reveal cortical thinning of the rib and disruption. On T1-weighted MRI they have low signal intensity. On T2-weighted MRI, they have high signal intensity, and fluid–fluid levels may be present.[5] Technetium-99m-hydroxymethylene diphosphonate bone scintigraphy reveals increased uptake by these lesions. Giant cell tumors metastasize approximately 5 percent of the time, with metastases most commonly to the lungs.[21] Metastases usually occur within 3 years of resection, but these have been reported to happen up to 8 years following resection of the primary tumor.[29]

Treatment is resection, when possible. Use of curettage with ablation of residual tumor via phenol, alcohol, or liquid nitrogen has been reported, as has been done for platinum-based chemotherapy for metastases.[21] The recurrence rate is approximately 50 percent, and adjuvant chemotherapy may be indicated to decrease this. Radiation therapy may be useful for treatment of these lesions; however, it is thought to impart a risk of malignant transformation, which may also occur rarely without radiation exposure.[30] Disease-free survival from pulmonary metastases from giant cell tumors of the bone is 56 percent at an average follow-up time of 8 years from diagnosis.[31]

## Malignant

### CHONDROSARCOMA

Chondrosarcomas are the most commonly occurring malignant primary tumors of the chest wall. They constitute approximately 24 to 40 percent of sarcomas of the chest wall in most large series.[3,32] They most commonly arise in the pelvis or long bones, and less frequently in the chest wall. However, when occurring in the chest wall, most develop in the anterior chest, arising from the costochondral arches of the ribs in 80 percent of occurrences and from the sternum in 20 percent of occurrences.[16] Although this tumor is thought to be related to prior chest wall trauma, 10 percent of chondrosarcomas develop from benign tumors of the cartilage. Extraosseous chondrosarcomas develop infrequently.[33] Chondrosarcomas occur in a bimodal distribution in patients younger than 20 years of age and in patients older than 50 years of age, with a male-to-female ratio of 2:1.

When large enough, chondrosarcomas are visible on chest radiograph.[34] They vary in degree of differentiation, resulting in a spectrum of appearances, with characteristics of various density and various patterns of calcification, irregular borders, and bone destruction. They are best visualized on CT (Fig. 18-14); however, on T1-weighted MRI chondrosarcomas have a signal intensity similar to muscle, with varying degrees of calcifications throughout.



**FIGURE 18-14** Representative image from CT scan of the chest of an 80-year-old man presenting with a slow-growing mass involving his right fourth through sixth ribs. Needle biopsy failed to confirm diagnosis. Surgical pathology revealed grade I chondrosarcoma. (Image courtesy of Douglas Wood, MD.)




**FIGURE 18-15** Photograph of the resected 11.4-cm grade I chondrosarcoma specimen from the chest of an 80-year-old man presenting with a slow-growing mass involving his right fourth through sixth ribs. Area of resection extends from the superior border of the third intercostals space superiorly, to the upper border of the seventh rib, medially from the sternal border to a clearly uninvolved margin laterally, and from the subcutaneous tissue to the adjacent pericardial fat pad including a deep border of a wedge resection of the right lower lobe. The overlying skin was preserved. Note the smooth surface of the mass. (Image courtesy of Douglas Wood, MD.)

On T2-weighted MRI, they have signal intensity similar to, or greater than, that of fat. The myxoid variant of chondrosarcomas lacks bone formation and calcifications, and may appear to have an increased signal intensity on T2-weighted MRI.[35]

Pathologic diagnosis can be made by core-needle biopsy. Chondrosarcomas are resistant to chemotherapy and radiation therapy. Treatment is surgical resection with negative tissue margins of at least 4 cm.[3,36] Local recurrence is reported in 17 percent of patients who were treated with wide resection, with a 96-percent 10-year disease-specific survival. Worse outcome is associated with incomplete or local excision, advanced tumor grade, and increased tumor size.[36] Evidence of invasion during resection can help differentiate low-grade chondrosarcomas from chondromas (Fig. 18-15).

## OSTEOSARCOMA

Osteosarcomas are one of the more commonly presenting chest wall sarcomas. In conjunction with chondrosarcomas, they constitute approximately 40 percent of sarcomas of the chest wall.[32] In the chest, osteosarcomas most frequently occur in the ribs, scapula, and clavicle. They most frequently present in young adults, commonly as a painful mass. Extraosseous osteosarcomas present in the sixth decade of life. Thoracic osteosarcomas spread locally and have a greater preponderance to recur and metastasize than extremity osteosarcomas. They may have cystic components in addition to heterogeneous bone matrix.

On chest radiograph, osteosarcomas appear as a mass with calcifications, lytic lesions, or sclerotic bone, described as a "sunburst" appearance. On CT, osteosarcomas appear to have calcifications in their centers, with heterogeneous enhancement on intravenous contrast studies. Osteosarcomas have a signal intensity greater than muscle on T1-weighted MRI, and high signal intensity on T2-weighted MRI.[35]

Osteosarcomas are treated with neoadjuvant chemotherapy followed by surgical resection. Prognosis is predicted by tumor response to chemotherapy.

## EWING SARCOMA AND PRIMITIVE NEUROECTODERMAL TUMOR

Characteristically presenting in children and adolescents, Ewing sarcoma makes up approximately 6 percent of malignant chest wall tumors.[3] Although constituting only 10 percent of cases of all Ewing sarcomas, Ewing sarcoma of the chest wall is the most common malignant lesion of the ribs in children. Ewing sarcoma and primitive neuroectodermal tumors, the latter of which constitutes less than 1 percent of chest wall sarcomas, are related along the continuum of cell differentiation as Ewing's sarcoma develops from neural crest cells as a solitary mass or multiple masses.[37] In the chest, they can occur in bones or as extraosseous lesions. They are aggressive tumors, which may displace or invade adjacent tissues, including the lung.

On chest radiograph, Ewing sarcoma classically has an "onion peel" appearance. On axial imaging, it appears as an ill-defined mass, with cystic degeneration, necrosis, and sometimes with calcifications. On T1-weighted MRI, Ewing sarcoma has a signal intensity equal to or greater than muscle, a high signal intensity on T2-weighted MRI, and it is contrast enhancing.[35]

The 5-year overall survival is equal to the 5-year cause-specific survival, at 44 percent in patients with nonmetastatic Ewing sarcoma following surgical resection, with or without adjuvant chemotherapy.[38] Chemotherapeutic agents used are generally vincristine, doxorubicin or adriamycin, and cyclophosphamide-based agents; however, etoposide and ifosfamide are gaining use.[39,40] Radiation therapy is used preoperatively for tumors considered "borderline" for successful resection and postoperatively for control of local disease in the setting of positive margins and local invasion into adjacent structures. Favorable local control rates indicate that patients primarily succumb to metastatic disease despite success of local resection.

## PRIMARY PLEUROPULMONARY SYNOVIAL SARCOMA

Synovial sarcomas, which have a mesenchymal origin, predominantly occur at para-articular locations in the extremities of young patients, but rarely occur in the chest wall, pleura, lung, or heart. These soft-tissue masses infiltrate adjacent structures if not diagnosed early.[41] Patients usually present in the second to fifth decade of life. Disease can

progress rapidly as these malignancies tend to be aggressive when occurring in the chest wall.

On CT imaging, synovial sarcomas appear as ill-defined masses with attenuation slightly greater than muscle, and calcifications may be present in approximately one-third of tumors. On T1-weighted MRI, synovial sarcomas have signal intensity equal to muscle, and may reveal foci of hemorrhage or fluid–fluid levels. On T2-weighted MRI, synovial sarcomas appear heterogeneous and may have internal septation visible.[35]

Treatment is comparable to that of other sarcomas, with wide resection. Case reports detail local recurrence within 1 year of initial resection, with mixed response to chemotherapy and radiation therapy.[42–44]

### ADAMANTINOMA

Adamantinomas are intraosseous epithelial neoplasms of low-grade malignancy. They are of uncertain histopathogenesis. Adamantinomas are rare, constituting 0.3 to 0.4 percent of all primary bone tumors.[45] Although most of these occur in long bones, with 60 to 90 percent occurring in the tibia, cases have been reported of primary adamantinomas occurring in the ribs.[45–47] They are slow-growing tumors, composed of epithelial and osteofibrous components in varying proportions, and have characteristic solid cell nests. They can invade adjacent tissues and become metastatic, with one of the three described primary rib tumors metastasizing to the liver.[47]

Adamantinomas present throughout life, with a mean age of 30 years. Patients present with a slow-growing mass on the rib, which may be painless or associated with dull pain. On radiologic imaging, adamantinomas appear as medullary, osteolytic, eccentric lesions with sclerotic margins.[47] On pathologic examination, adamantinomas may be confused with epithelial metastatic neoplasms and sarcomas. They can be differentiated from other tumor types via immunohistochemical staining for markers of epithelial origin. Treatment is wide resection, with recurrences and metastases most commonly to lungs and abdominal viscera occurring up to 15 years after resection. Postoperative survival of patients with adamantinomas, irrespective of tumor site, is 82.5 percent after 4 years.[48]

## MUSCLE

## Benign

### LEIOMYOMA

The development of leiomyomas, benign tumors originating from smooth muscle, in the chest wall is exceedingly rare. In the only recent case report, a leiomyoma arose from the microvascular smooth muscle in the extrapleural chest wall of a 55-year-old female, and was successfully treated with resection.[49]

### RHABDOMYOMA

Rhabdomyoma of the chest wall has only been reported as isolated case reports, treated with surgical resection.

## Malignant

### LEIOMYOSARCOMA

Leiomyosarcoma of the chest wall represents between 1 and 5 percent of primary soft-tissue chest wall sarcomas.[3,32,37,50] It most commonly presents in men, in the sixth to eighth decade of life, as a painful mass, or is incidentally found on imaging studies. Epstein–Barr virus is associated with the development of leiomyosarcomas as well as leiomyomas, in patients with AIDS, and leiomyosarcoma may develop secondary to exposure to cyclophosphamide.[51,52] In advanced cases, leiomyosarcoma may present with cutaneous or hepatic metastases.

On CT imaging, these malignancies lack calcification, but may have central necrosis or a cystic appearance, and may displace adjacent vascular structures. On MRI, they present as spindle-shaped lesions. On T1-weighted MRI, they have low signal intensity, while on T2-weighted MRI, they have high signal intensity. With intravenous contrast, leiomyosarcomas typically have a rim-enhancing appearance (Figs. 18-16, 18-17, and 18-18).[35] Pathologic diagnosis can be confirmed via the presence of spindle cells, staining positive for vimentin. Treatment and outcomes are comparable with that of other soft-tissue sarcomas discussed later in this chapter.

### RHABDOMYOSARCOMA

Rhabdomyosarcoma constitutes approximately 11 percent of malignant chest wall tumors, and represents the second

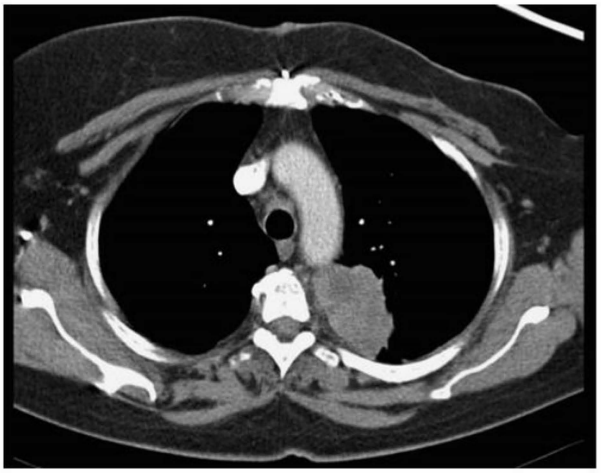


**FIGURE 18-16** CT image of a 59-year-old woman with a 4.5 × 3.6 × 3.4 cm chest wall leiomyosarcoma that had invaded into adjacent chest wall structures as well as adjacent lung parenchyma. (Image courtesy of Douglas Wood, MD.)

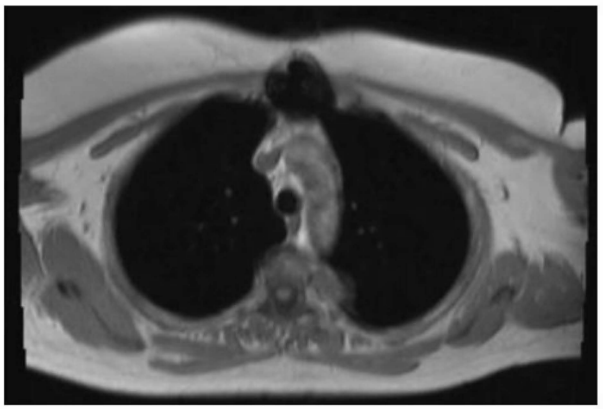


**FIGURE 18-17** The same chest wall leiomyosarcoma from Figure 18-16 imaged with T1-weighted MRI. (Image courtesy of Douglas Wood, MD.)

most commonly identified malignant chest wall tumor in children.[3] It is a high-grade sarcoma with differentiated skeletal muscle. Rhabdomyosarcoma presents before middle age with a rapidly growing mass, or with symptoms related to mass effect. Bone invasion occurs in a fifth of patients with rhabdomyosarcoma. Different subtypes of rhabdomyosarcoma exist, with the alveolar subtype occurring the most frequently in the chest wall.[53] On CT and MRI, it lacks calcifications, may have central necrosis, and has a heterogeneous appearance on T1- and T2-weighting.[35]

Treatment is comparable with that of other sarcomas, with wide resection being the mainstay of therapy. Chemotherapy is used based on institutional experience and preference. Radiation therapy is reserved for tumor-positive margins following surgical resection. Metastases occur in two-thirds of patients with rhabdomyosarcoma of the chest wall.[37]

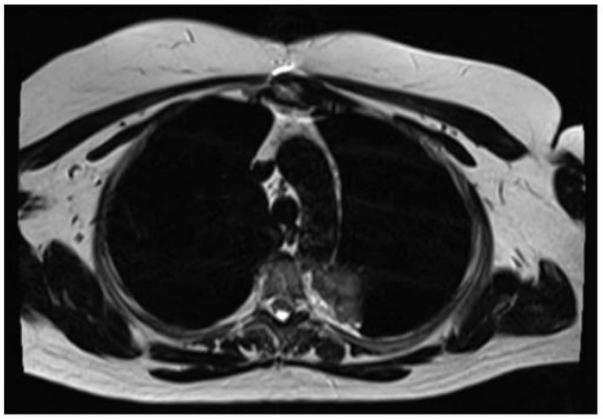


**FIGURE 18-18** The same chest wall leiomyosarcoma from Figure 18-16 imaged with T2-weighted MRI. (Image courtesy of Douglas Wood, MD.)

# NERVE

## Benign

### NEUROFIBROMA

Neurofibromas originate from a nerve and are slow-growing in nature. They typically present in patients in their third to fourth decade of life. They may or may not be encapsulated. Sixty to ninety percent of patients with neurofibromas have neurofibromatosis type 1 (NF-1) or multiple plexiform neurofibromas.

On axial imaging, they present as well-defined lesions with plexiform contours, calcifications, and may have adjacent rib erosion. They have variable contrast enhancement on intravenous contrast CT imaging. On T1-weighted MRI, neurofibromas have low signal intensity, while in T2-weighted imaging, they have high signal intensity peripherally due to enhancement of the peripheral stromal architecture and lack of enhancement by the central cellular component, resulting in a target-like appearance.[5] When gadolinium is administered, the center of the tumor is enhanced on MRI.[54] Rarely they may progress to malignant degeneration. Treatment is surgical excision for symptomatic lesions and to rule out malignant disease.

### SCHWANNOMA

Schwannomas develop from schwann cells, which form nerve sheaths and facilitate nerve-signal conduction. In the chest, schwannomas typically arise from intercostal nerves and spinal nerve roots (Fig. 18-19). They are characteristically encapsulated, well circumscribed, firm, spheroid, or ovoid masses (Fig. 18-20). Malignant schwannomas, or malignant peripheral nerve sheath tumors, constitute less than 10 percent of chest wall schwannomas, and therefore, suspicion of

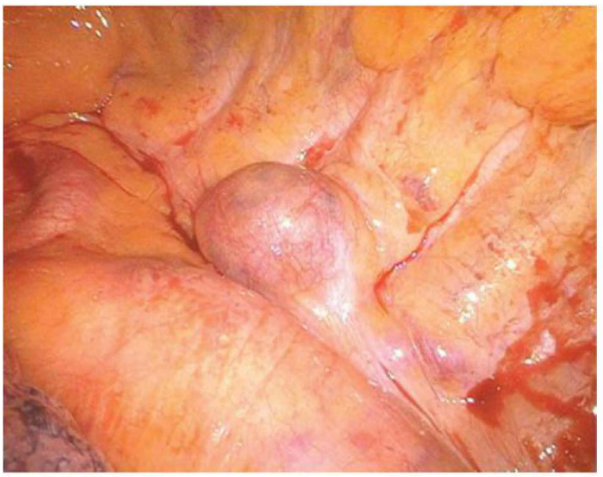


**FIGURE 18-19** Intraoperative photograph of a schwannoma occurring on the left chest wall just lateral to the aortic arch. (Image courtesy of Leah Backhus, MD.)

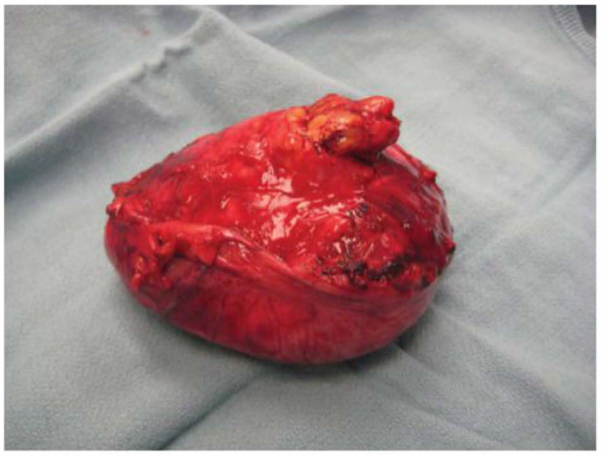


FIGURE 18-20 Photograph of resected 10.5 × 9.6 × 5.5 cm schwannoma specimen from a 34-year-old man identified initially on chest radiograph for pain. Note the intercostal nerve root protruding from the tumor. (Image courtesy Douglas Wood, MD.)

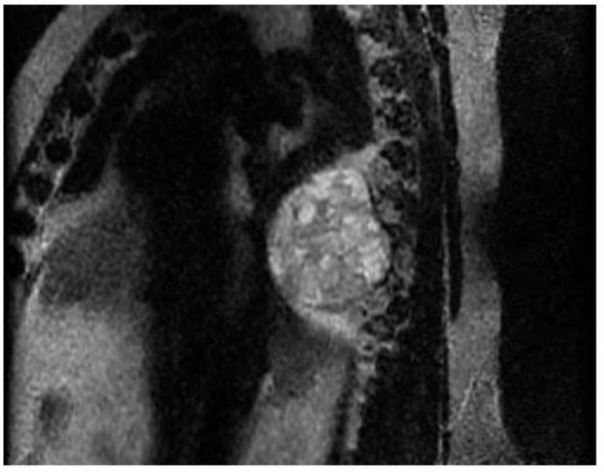


FIGURE 18-22 Sagittal view of a chest wall Schwannoma imaged with T2-weighted MRI. (Image courtesy of Douglas Wood, MD.)

malignancy should be maintained during workup and initial resection.[55]

Schwannomas are slow-growing and typically present in patients in their third through sixth decades of life. On axial imaging, schwannomas appear as well-defined lesions adjacent to nerves. Nonenhancing central necrosis may be present in larger lesions, and bone erosion may be present as well, indicating the presence of smaller lesions. On both T1- and T2-weighted MRI, larger schwannomas have a heterogeneous signal due to cystic change within the tumor, whereas smaller lesions are homogeneous. However, although their signal intensity on T1-weighted MRI is slightly more than that of muscle, it is greater than muscle on T2-weighted MRI (Figs. 18-21, 18-22, and 18-23).[5] Of note, they are painful to biopsy percutaneously. Treatment is surgical excision for symptomatic lesions and also serves to rule out malignant disease. Due to possible central neural involvement, we advocate resection in conjunction with a neurosurgeon who has evaluated the patient preoperatively.

## PARAGANGLIOMA

Paragangliomas of the chest wall arise from paraganglial cells of the aorticosympathetic or aorticopulmonary paraganglia, in the paravertebral region of the fifth, sixth, or seventh ribs. They occur on the right more than in the left, and present in late childhood to early adulthood. Although approximately 95 percent are nonfunctioning, they may rarely be functional pheochromocytomas, producing excess catecholamines. Patients may present with synchronous or metachronous extrathoracic paragangliomas.

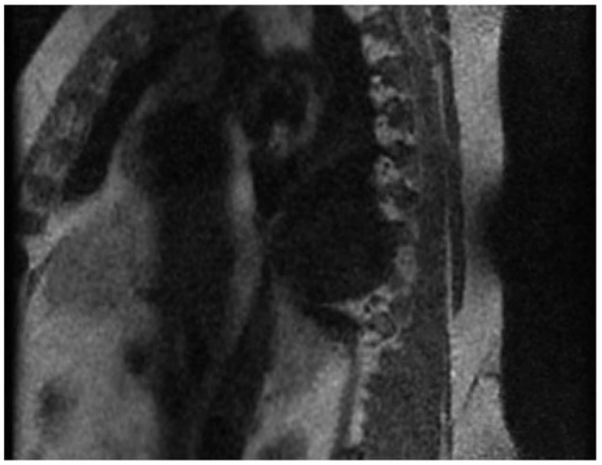


FIGURE 18-21 Sagittal view of a chest wall Schwannoma imaged with T1-weighted MRI. (Image courtesy of Douglas Wood, MD.)

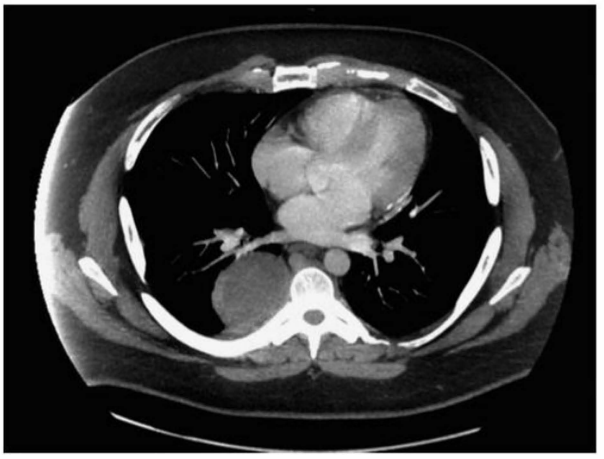


FIGURE 18-23 Axial view of a chest wall Schwannoma imaged with CT. (Image courtesy of Douglas Wood, MD.)

On axial imaging, paragangliomas appear as well-defined lesions in a midthoracic location. They are homogeneous in appearance and have intravenous contrast enhancement.[56] On T1-weighted MRI, paragangliomas have low signal intensity, whereas on T2-weighted imaging they have high signal intensity.[5]

Workup includes a 24-hour urine metanephrine test to determine if tumors are metabolically functional. Although both nonfunctioning and functioning tumors should be excised, the preoperative treatment algorithm for pheochromocytomas holds true for those occurring in the chest. This entails 2 weeks of preoperative alpha-blockade, with volume resuscitation on the order of several kilograms of gained weight, followed by beta-blockade. Treatment is surgical resection for symptomatic lesions and to rule out malignant disease.

### GANGLIONEUROMA

Ganglioneuromas of the chest wall arise from sympathetic chain ganglia in the chest wall, are composed of mature ganglion cells as well as Schwann cells, and are located paravertebrally and in the posterior mediastinum. They present in early adulthood, with a median age at diagnosis of 7 years, with a slight female preponderance.[57]

Ganglioneuromas are slow-growing and encapsulated. As such, they are most commonly found incidentally on radiographic study for other purposes (e.g., trauma evaluations), but patients may present with dyspnea or cough. On axial imaging, they appear as well-defined lesions, with calcifications present in approximately one-quarter of patients. On CT imaging, they may have either heterogeneous or homogeneous attenuation. On T1- and T2-weighted MRI, ganglioneuromas have areas of low signal intensity, creating a whorled appearance.[5]

They rarely metastasize, with reported metastatic ganglioneuromas likely representing neuroblastomas or ganglioneuroblastomas that have matured to ganglioneuromas, and confer an excellent prognosis in comparison with the more undifferentiated neuroblastic tumors. Rarely, ganglioneuromas may be metabolically active, necessitating workup and management as discussed for paraganglioma-pheochromocytomas earlier. Treatment of ganglioneuromas is complete surgical resection, in part to minimize risk of recurrence, and in part to enable thorough pathologic examination to rule out malignant neuroblastic tumors, such as neuroblastoma and ganglioneuroblastoma, which would possibly necessitate additional therapy.

## Malignant

### NEUROFIBROSARCOMA AND MALIGNANT PERIPHERAL NERVE SHEATH TUMOR (MALIGNANT SCHWANNOMA)

Previously known as malignant schwannomas, and alternately known as neurogenic sarcomas, malignant peripheral nerve sheath tumors occur throughout the body, along the course of peripheral nerves, and present during adulthood. They constitute less than 10 percent of chest wall tumors and approximately 9 to 13 percent of chest wall sarcomas.[3,32,37] Fifty percent of cases are associated with NF-1, where they occur in a male-to-female ratio of 4:1 and present in younger patients. Patients with NF-1 have a lifetime risk estimated at 10 percent of developing malignant peripheral nerve sheath tumors.[55,58,59] These tumors may develop de novo, or from preexisting neurofibromas. Although these are the most common mediastinal neurogenic tumors, they may involve any myelinated nerve, and therefore, approximately 5 percent of thoracic malignant peripheral nerve sheath tumors occur in the chest wall, usually from intercostal nerves.[59]

Patients with malignant peripheral nerve sheath tumors of the chest wall present with localized pain. Masses are slow-growing and may project into the thoracic cavity. On CT, malignant peripheral nerve sheath tumor appears as a well-circumscribed heterogeneous mass and may be associated with adjacent boney destruction if occurring on an intercostal nerve. On T1-weighted MRI, these have heterogeneous signal intensity greater than that of muscle, while on T2-weighted MRI, they have heterogeneous high signal intensity. They are difficult to distinguish from benign neurofibromas.[35] Four-quadrant open biopsies are preferable to percutaneous needle biopsies for definitive diagnosis.[60]

For localized tumors, treatment is wide resection. Features associated with poor prognosis including tumor size greater than 5 cm, advanced histology, higher tumor grade, and association with NF-1. Malignant peripheral nerve sheath tumors carry a high risk of local recurrence as well as distant metastases, and therefore, a staging CT or MRI of the chest and abdomen is useful, as well as localized imaging studies for specific symptoms (e.g., CT of the head). The current management algorithm is surgical resection to negative margins, plus neoadjuvant or adjuvant radiation therapy, with optional addition of adjuvant chemotherapy. The role of tyrosine kinase inhibitors in treatment of malignant peripheral nerve sheath tumors is currently being studied. Overall 5-year survival is between 34 and 64 percent.[55,60]

### NEUROBLASTOMA AND GANGLIONEUROBLASTOMA

Neuroblastomas and ganglioneuroblastomas rarely occur in the chest wall, most frequently in children, in the extra-adrenal sympathetic ganglia, resulting in paraspinal tumors. They represent the undifferentiated continuum of tumors arising in the sympathetic ganglia from a neural crest cell origin. Neuroblastomas are composed of neuroblasts, undifferentiated neural crest cells. Ganglioneuroblastomas are composed of mature gangliocytes and immature neuroblasts. The presence of undifferentiated tissue predisposes these tumors to potentially malignant behavior, with that of neuroblastoma being greater than that of ganglioneuroblastoma. Their mature counterparts, ganglioneuromas, are of low malignant potential.

Neuroblastoma is one of the most common pediatric malignancies in the United States, with a median age of presentation of 22 months, regardless of tumor site. Presenting symptoms include chest and shoulder pain, Horner syndrome, a painless mass, and opsoclonus-myoclonus, or jerking of the extremities and eyes most commonly associated with thoracic primary neuroblastomas.[57,61]

Chest wall neuroblastomas and ganglioneuroblastomas appear as poorly defined tumors, often with calcifications. On T1-weighted MRI, these have heterogeneous low signal intensity, while on T2-weighted MRI, they have heterogeneous high signal intensity.[35] Approximately 15 percent of neuroblastomas arising from the paraspinal sympathetic chain extend intrathecally, which can be seen on noncontrast MRI.[62] Therefore, at surgical resection, we prefer to seek the assistance of an experienced neurosurgeon, should there be spinal involvement. The aim of surgical extirpation is resection with macroscopically negative margins.

Disease-free and overall survival is related to tumor stage. Treatment of stage III tumors may benefit from neoadjuvant chemotherapy. More advanced-stage tumors should be treated with definitive chemotherapy, with radiation therapy added for node-positive disease. Metastases most commonly occur to bone and have varying degrees of response to chemotherapy.[57]

# LYMPHOVASCULAR

## Benign

### CAVERNOUS HEMANGIOMA

Cavernous hemangiomas occur in utero and present at birth or before the third decade of life. They present as a mass of dilated, tortuous, thin-walled vessels usually in the skin, but in the chest wall they are associated with intercostal locations and resulting erosion into adjacent bone, namely, the ribs and sternum.[63]

Hemangiomas of the chest wall are typically found incidentally on radiographic chest imaging, or as a palpable mass. On CT imaging, cavernous hemangiomas characteristically appear with ill-defined contours and enhancement on intravenous contrast studies. One-third develop phleboliths, which are visible on CT.[64] On MRI, they may appear to have heterogeneous signal intensity, fluid–fluid levels, and areas of high signal intensity on both T1- and T2-weighted images.[5]

Because many chest wall tumors with a similar presentation are malignant, to avoid risk of seeding tumor cells along a needle-biopsy tract, needle biopsy should be avoided. Preoperative biopsy should only be performed when tissue diagnosis will dictate management, for example, on lesions larger than 5 cm, where complex reconstruction following complete resection is anticipated, and when lymphoma, multiple myeloma, or tumor metastases are suspected. Otherwise, excisional biopsy should be performed. Nonsurgical treatment options include observation, and embolization, specifically where hemangiomas are superficial.[65]

### GLOMUS TUMOR (GLOMANGIOMA)

Glomus tumors are rare tumors that develop in adulthood, with equal frequency in women and men. They are often intramuscular and present with a solitary painful lesion, but may also present as multiple painless lesions.[66] They develop from the glomus body, specialized smooth muscle cells involved with thermoregulation at arteriovenous anastomoses.

CT imaging characteristically reveals well-defined contours around an enhancing soft-tissue mass with feeding vessels and associated bone erosion. MRI is characterized by heterogeneous signal intensity on both T1- and T2-weighted images; the tumor displaces vessels and is surrounded by feeding vessels and hence is well-defined on contrast studies.[5] Treatment is surgical resection for symptomatic lesions and to rule out malignant disease.

### LYMPHANGIOMA (CYSTIC HYGROMA)

Lymphangiomas are benign congenital lymphomatous malformations. They most commonly present in the neck, but may involve the chest wall, in neonates. Large lesions may be visualized on prenatal ultrasonography.[67] Differentiation from solid masses and diagnosis is aided by the ability to transilluminate characteristically balotable lesions, and by the presence of a multiloculated cystic mass on ultrasound. Although benign, lymphangiomas may develop complications when they become large and compress adjacent anatomy, if they hemorrhage, fistulize, or become infected. Surgical resection is indicated for large lesions, when there is risk of complication, and may require multiple stages. Lymphangiomas may recur with incomplete resection.[68]

## Malignant

### ANGIOSARCOMA

Angiosarcoma constitutes approximately 4 percent of chest wall sarcomas.[3,32] These malignant endothelial neoplasms present as painful, enlarging masses, with a peak incidence in the seventh decade of life. In a series of 80 patients with angiosarcoma, 14 percent had lesions involving the trunk wall including the chest wall.[69] Angiosarcomas are associated with chronic lymphedema, and radiation and chemical exposure (specifically arsenic, thorium dioxide, and polyvinyl chloride). They rarely occur in the chest, but can occur in proximity to the breast in men and women, usually following radical-surgical or radiation therapy for carcinoma of the breast.

As these lesions are highly vascular, they enhance on CT and MRI with intravenous contrast administration, when feeding vessels may be visualized. The associated

lymphedema is characterized by soft-tissue nodules and fluid collections adjacent to muscle, and increased attenuation of fatty tissue.[35] Complications include anemia, hemorrhage, and coagulopathy.

Treatment is similar to that of soft-tissue sarcomas, discussed in detail later, and entails wide resection. Local recurrences occur in approximately 20 percent of patients, with a median disease-free interval of 7 months. Metastases occur in 49 percent of patients. Overall 50 percent survival is 20 months.[69]

## SOFT TISSUE (FAT AND SKIN)

### Benign

#### LIPOMA

Lipomas are encapsulated benign growths of adipocytes. They commonly present in a wide age range of adulthood. On CT imaging, they characteristically appear as well-defined nonenhancing homogeneous masses. On T1- and T2-weighted MRI, they have high signal intensity, with low signal intensity of thin septa that may be present.[5] A key point of surgical management is extracapsular resection to minimize the likelihood of local recurrence. Seldom is reconstruction required following resection of lipomas, as overlying skin and adjacent tissue can be preserved.

#### ELASTOFIBROMA

Elastofibromas are common, slow-growing benign chest wall lesions that characteristically develop deep to the scapula. They are considered "pseudotumors" as they form due to fibroblastic proliferation. They are reported in approximately 10 to 25 percent of cadavers on autopsy. They occur in the inferior subscapular region, deep to the serratus anterior, latissimus dorsi, and rhomboid muscles. Ten percent occur bilaterally.[70]

Although most elastofibromas are asymptomatic, symptomatic patients present with shoulder discomfort or pain. On CT imaging, they appear as poorly circumscribed soft-tissue masses with signal intensity similar to muscle. On T1- and T2-weighted MRI, they have low signal intensity, with intervening high signal fat strands. On PET-CT, elastofibromas have increased metabolic activity with FDG uptake, which may lead to misdiagnosis of malignancy. Core-needle biopsy may be diagnostic.[70]

Treatment of symptomatic lesions is excision, and radiologic and tissue diagnosis should be confirmed prior to radical resection for misdiagnosis of malignancy.

#### OTHER BENIGN SOFT-TISSUE TUMORS

Other benign soft-tissue tumors have been described as involving the chest wall. These are usually reported as solitary cases. Included among these are chondroid syringoma, a benign, slow-growing tumor of the eccrine and apocrine glands, with mixed epithelial and mesenchymal elements. Although these more commonly arise from salivary glands, they may occur in the axilla. These usually present as slow-growing, painless nodules of the head and neck, most commonly seen in middle-aged or older men. Rarely, these may undergo malignant transformation or metastasis.[71]

Diagnosis of these rare tumors presents a challenge, and is often made after surgical biopsy or resection. Treatment is margin-negative excision, and wide local resection if suspicion exists for malignancy and for tumors larger than 3 cm. Regional lymph nodes should be sampled if they are clinically palpable or suspicious.

### Malignant

#### SOFT-TISSUE SARCOMA

Sarcomas of the chest wall are rare. Presentation is typically due to development of a nonpainful mass, and less frequently a painful mass, pain alone, or as an incidental finding on radiographic imaging.[37] In addition to infiltration of adjacent structures, symptoms may be due to local compression and present as limb paresthesias, range of motion defects, and distal swelling of a compromised upper extremity.[72] Diagnosis is made by core-needle biopsy or open biopsy. For superficial lesions less than 5 cm in diameter, excisional biopsy is used. Contrast enhanced MRI is our preferred method of evaluation of extent of the tumor (Fig. 18-24). In addition, CT of the chest should be obtained during workup for staging to rule out pulmonary metastases and regional and mediastinal lymphadenopathy. In cases of the latter, either mediastenoscopic lymph node sampling or PET scan is useful for lymph node staging.

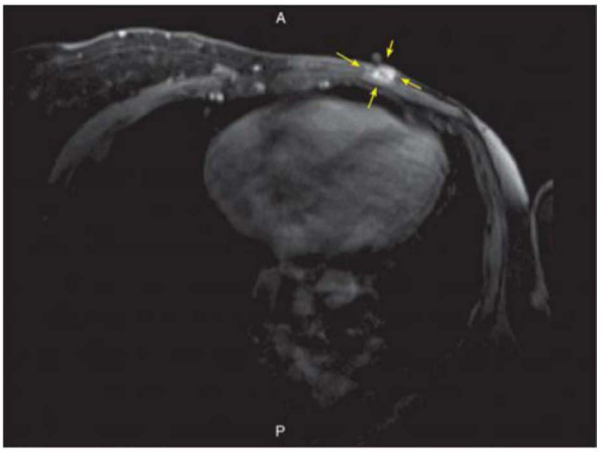



**FIGURE 18-24** Representative image from MRI scan of the chest of patient with recurrent sarcoma of the chest wall. The arrows mark the site of chest wall recurrence. (Image courtesy Merhan Habibi, MD.)

The goal for surgical extirpation of soft-tissue sarcomas is en bloc full-thickness chest wall resection with a 1-cm margin of normal tissue to achieve tumor-free (R0) margins. On definitive resection, the biopsy tract, including overlying skin incision site, should be excised with the specimen. The achievement of a 1-cm tumor margin may pose a technical challenge, based on anatomic relation of the tumor to adjacent structures. Grossly, tumor-positive (R2) margins necessitate reresection. When technically feasible, reresection should be performed for microscopically positive (R1) margins. Regional lymph nodes should be examined for metastases, as this may affect postoperative treatment and prognosis.

Neoadjuvant radiation therapy (50 Gy) can be used to diminish burden of disease with large tumors and improve the ability to obtain tumor-free margins for tumors involving vital structures (nerves and blood vessels). Intraoperative radiation therapy and brachytherapy may be considered for some situations, highlighting the utility of multidisciplinary management of soft-tissue sarcomas from early on in patient management.

Radiation therapy (50–60 Gy) is added postoperatively for residual disease, tumor margins less than 1 cm, tumors larger than 5 cm, or highly invasive tumors.[73,74] In the instance of intracompartmental tumors treated via compartmental resection, radiation therapy is not strictly indicated.

No consensus has been reached on the utility of chemotherapy for the primary treatment of soft-tissue sarcomas. Chemotherapy is used for recurrent disease and for metastatic disease. Intraoperative brachytherapy is used selectively to sterilize deep close margins.

Local recurrence of soft-tissue sarcomas occurs in up to two-thirds of patients, and should be treated with reresection when possible, and radiation therapy should be considered.[37,75] In a large series of chest wall soft-tissue sarcomas, approximately 7 percent of patients presented with synchronous metastases, and ultimately 35 percent experienced metastases.[37] Lung metastases from sarcomas should be treated with chemotherapy, especially in the setting of synchronous lesions in the absence of extrapulmonary disease.[73] However, isolated pulmonary lesions can be treated with wedge resection. In select populations, the latter confers up to 20 percent 5-year survival.[76]

Rapidity of disease recurrence is a function of malignancy grade and response to, and completeness of, definitive therapy. Recurrence is seen within 2 to 3 years in high-risk patients. To achieve early detection of local or pulmonary recurrence, we advocate regular follow-up visits with CT of the chest at 4-month intervals for the first 2 to 3 years after treatment, then every 6 months up to 5 years, and yearly thereafter.

Overall 5-year survival of chest wall soft-tissue sarcomas is 66 percent, with significantly poorer 5-year survival for those with high-grade sarcomas (49 percent) as compared with those with low-grade sarcomas (90 percent).[37] In a series of patients treated with chest wall resection for high-grade sarcomas, either primary, metastatic, or recurrent, 5-year disease-free survival was 40 percent and overall 5-year survival was 59 percent, suggesting that aggressive surgical resection to establish tumor-free margins should be performed for chest wall sarcomas.[50] Another study reported similar results with a 50 percent 5-year survival following chest wall resection for recurrent sarcomas.[32]

## DESMOID TUMOR

Desmoid tumors involving the chest wall account for between 20 and 50 percent of low-grade chest wall sarcomas.[2,3,37,77–81] Desmoid tumors, also known as fibromatosis, are fibroblastic and myofibroblastic neoplasms. These histologically benign tumors arise from the connective tissue of the muscular aponeurosis, and are locally aggressive, invading adjacent structures, but usually confined to musculature and fascia. Although they most commonly occur in the abdomen, the retroperitoneum, and the extremities, approximately 20 percent of desmoid tumors occur in the chest wall and intrathoracically.[82,83] On histologic examination, desmoid tumors have characteristic spindle cells separated by thick bands of collagen. These are associated with beta-catenin, adenomatous polyposis coli germline, or somatic mutations.[82] They more frequently occur in females, patients with familial adenomatous polyposis, and at sites of prior trauma or scaring, such as rib fractures.[81] They characteristically present as an enlarging mass, which becomes painful due to compression and invasion of local structures, including the lungs.[84]

Radiologic appearance varies and is based on collagen content of the tumor, and may be infiltrative or nodular in nature. Desmoid tumors are best characterized by T1-weighted MRI, where they have a signal intensity less than or comparable to muscle, and T2-weighted MRI, which can elucidate soft-tissue infiltration (Figs. 18-25 and 18-26).[35]

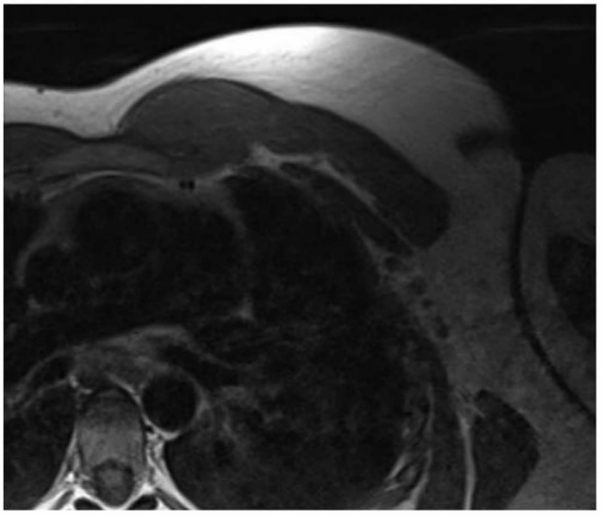


**FIGURE 18-25** T1-weighted MRI of left chest wall desmoid tumor in a 20-year-old woman. (Image courtesy of Douglas Wood, MD.)

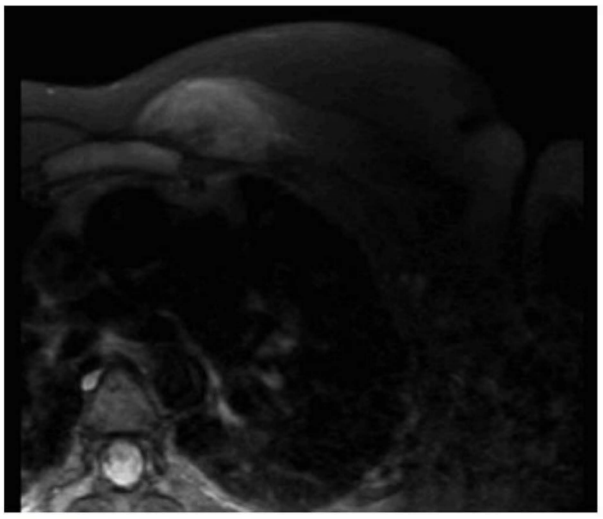


**FIGURE 18-26** T2-weighted MRI of left chest wall desmoid tumor in a 20-year-old woman. (Image courtesy of Douglas Wood, MD.)

However, desmoid tumors may not be well characterized on CT imaging (Fig. 18-27). In addition, open biopsy may not yield a correct diagnosis.

Treatment is radical resection with microscopically negative margins (R0) of 2 to 4 cm.[82,85] The inability to achieve microscopically negative tissue margins may result in the need for radiation, which may be given pre- or postoperatively, or in lieu of surgery due to the inability to resect lesions based on anatomic constraints. Chemotherapy, anti-inflammatory therapy, and hormone therapy are reserved for situations where surgical resection is not an option, such as widespread tumor infiltration. No single agent or combination chemotherapy has been identified that elicits a response in all patients. Agents noted to induce a partial or complete response in patients include doxorubicin and dacarbazine, interferon-alpha with or without tretinoin, vinorelbine or vinblastine and methotrexate, and tamoxifen.[82,86]

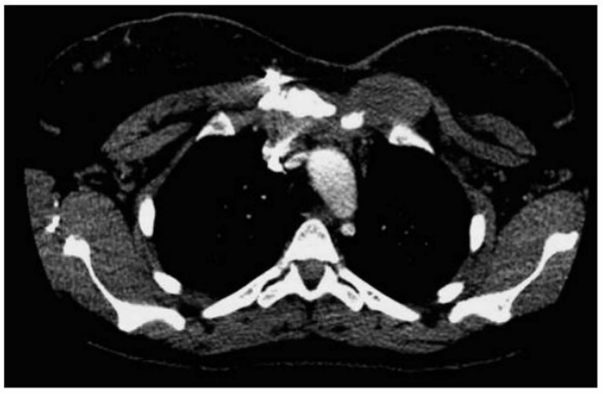


**FIGURE 18-27** Chest CT of the same patient in Figures 18-25 and 18-26 one year after initial resection of chest wall desmoid tumor and medial head of left clavicle, and subsequent reconstruction. Recurrence of the desmoid tumor is evident, as is hardware from initial reconstruction. (Image courtesy of Douglas Wood, MD.)

Although between one-quarter and one-half of desmoid tumors recur locally following resection, they do not metastasize. Recurrence is associated with degree of resection. In a series of 53 patients who underwent surgery for chest wall desmoid tumors, 89 percent recurrence rate was reported in patients with micro- or macroscopically positive resection margins. Fifty percent of patients who underwent reresection developed local recurrence, as opposed to only 8 percent of those who underwent margin-negative primary resection. The 5-year local recurrence rate is between 29 and 37.5 percent, with 5-year survival of 93 percent.[87,88] Lifelong follow-up with imaging and biopsy of suspicious lesions is necessary to rule out recurrence and malignancy.

## PROXIMAL-TYPE EPITHELIOID SARCOMA

Although proximal-type epithelioid sarcoma, an undifferentiated soft-tissue sarcoma, characteristically occurs in the extremities, attached to tendon, tendon sheaths, or fascia, they may occur in the chest wall.[89] These present as a subcutaneous or deep dermal mass. Proximal epithelioid sarcomas, occurring in the trunk and thighs, are more aggressive than those occurring in the distal extremities. Histologically, they resemble poorly differentiated carcinoma with sheets of large cells with characteristic prominent nucleoli, and frequently have a rhabdoid phenotype.

On CT imaging, approximately one-third of these tumors have stippled calcification. On T1-weighted MRI, proximal-type epithelioid sarcomas have signal intensity equal to muscle. On T2-weighted MRI, they appear as heterogeneous masses with high signal intensity. They are intravenous contrast enhancing.[35] Immunohistochemistry is necessary to differentiate proximal-type epithelioid sarcoma from other epithelioid lesions.

Treatment is wide local excision. Chemotherapy and radiation therapy have been used pre- and postoperatively. In a series of 20 patients, with mean follow-up of 4 years and 5 months, there was a 65 percent local recurrence rate, and a mean disease-free survival of 10 months. The same authors report a 75-percent rate of metastases, with metastases to lymph nodes, the lung, bone, and skin.[89] Larger tumor size at presentation was correlated with poorer prognosis but not occurrence of metastasis.

## RADIATION-INDUCED SARCOMA

Radiation-induced sarcoma of the chest wall is an aggressive tumor, occurring in patients who have undergone radiation therapy for, and survived, breast cancer and lymphoma. Tumor types described include chondrosarcomas, osteosarcomas, fibrosarcomas, malignant fibrous histiocytomas (MFHs), malignant schwannomas, and undifferentiated sarcomas. In a series of 15 patients, interval between

radiation therapy and occurrence of radiation-induced sarcoma ranged between 6 and 27 years, with a median of 14 years.[90] Treatment entails aggressive wide local en bloc resection, including involved skin and soft tissue, previously irradiated tissue and surgical sites, with an R1 margin of 4 cm. Rib margins include the unaffected rib above and below the tumor, and involved viscera including lung and mediastinal structures are resected. High-grade tumors are treated with adjuvant chemotherapy. Median survival of surgically managed radiation-induced sarcoma is approximately 5 years.[90]

### MALIGNANT FIBROUS HISTIOCYTOMA

Extrapleural MFH tumors are rare tumors of mesenchymal origin, accounting for 0.6 percent of soft-tissue tumors, and between 7 and 27 percent of malignant chest wall tumors in several large series.[3,37,91] They typically originate in skeletal muscle and fascia. MFH tumors develop malignant features in approximately 50 percent of cases.[13] Although they predominantly occur in the pleura, extrapleural locations include chest wall, head and neck, endocrine glands, intraperitoneally, and in the retroperitoneum. Extrapleural solitary MFH tumors have a higher rate of locoregional recurrence, as well as the possibility of metastasis. When occurring in the chest wall, they are more commonly located presternally.[37] Of the chest wall soft-tissue sarcomas, MFH are the least likely to metastasize, occurring in only 18 percent in one large series.[37]

On CT imaging, MFH appear as a heterogeneously enhancing mass in muscle or fascial planes (Fig. 18-28). The myxoid type of MFH has a characteristic appearance of central low attenuation of the myxoid matrix surrounded by enhancing nodular tissue on CT. Appearance on MRI may be variable, but on T1-weighted MRI, most MFH tumors have an appearance similar to muscle, while on T2-weighted MRI, they have the signal intensity equal or greater to that of adipose tissue.[35]

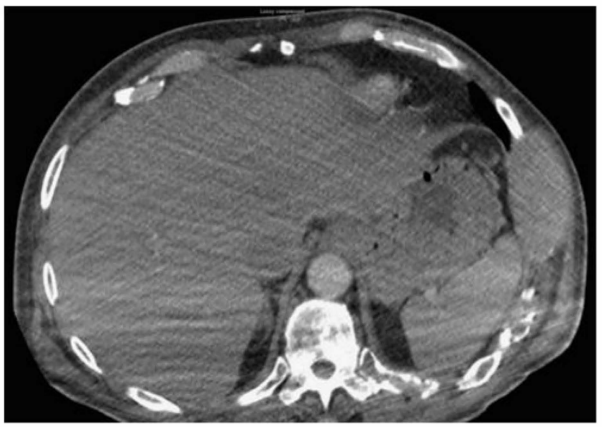


**FIGURE 18-28** Representative image from CT scan of the chest of 62-year-old man with an 8.5 × 4.1 cm malignant fibrous histiocytoma encompassing the left seventh through ninth ribs prior to resection. Following resection, reconstruction of the chest wall was achieved with 2 mm Gore Tex. (Image courtesy of Michael S. Mulligan, MD.)

As with other rare sarcomas, diagnosis of MFH should be confirmed by a pathologist experienced in soft-tissue tumors and well-established pathologic criteria of malignancy exist. Treatment is resection with negative margins, with adjuvant chemotherapy and radiation therapy for malignant disease, or for margin-positive disease where additional surgical resection is not an option. Extended long-term follow-up is warranted.

### LIPOSARCOMA

Liposarcoma constitutes 15 to 20 percent of adult chest wall sarcomas, and less than 10 percent of malignant chest wall tumors.[3,37] Three distinct clinicopathologic subtypes of liposarcoma exist: pleomorphic, myxoid, and well-differentiated or dedifferentiated liposarcoma. The latter is the most common subtype, accounting for 40 to 45 percent. Ten percent of liposarcomas present in the chest wall.[32] A recent series of 12 dedifferentiated liposarcomas reported one involving the chest wall, the majority occurring in the retroperitoneum.[92] On radiologic imaging, the different subtypes differ in appearance due to their histopathology. In general, as liposarcomas contain fat and soft tissue, they appear slightly more dense than fat on CT.[35] Treatment and outcomes are comparable with that of other soft-tissue sarcomas of the chest wall, which is already discussed.

### OTHER SARCOMAS

For other, rare soft-tissue malignancies, diagnosis should be confirmed by a pathologist experienced in soft-tissue tumors, as well-established pathologic criteria of malignancy exist for many tumors. These include spindle cell sarcomas, tenosynovial sarcomas, hemangiopericytomas, alveolar soft-part sarcomas, dermatofibrosarcoma protuberans, and giant cell sarcomas, each of which constitute less than 3 percent of chest wall soft-tissue sarcomas in a large series.[37]

### SKIN CANCER

Skin cancer may occur on the chest wall, with melanoma occurring particularly in areas of high sun exposure. Treatment is beyond the scope of this chapter and is discussed in-depth in other forums.

## HEMATOLOGIC

## Malignant

### LYMPHOMA

Primary lymphomas of the chest wall are rare in comparison with metastatic lymphoma, and account for approximately

1 percent of malignant chest wall tumors.[3] Primary lymphoma of the bone, accounting for approximately 5 percent of primary bone tumors, is usually diffuse histiocytic non-Hodgkin lymphoma. Secondary skeletal involvement occurs in up to 25 percent of patients with Hodgkin lymphoma, and approximately 20 percent of patients with non-Hodgkin lymphoma.[93]

Boney invasion may occur from hematogenous dissemination or spread from adjacent diseased lymph nodes. Sternal involvement is commonly due to direct extension from internal mammary lymph nodes. Differentiation between primary disease and metastatic disease is critical to staging and treatment, with metastatic lesions conferring stage IV disease.

Lymphoma involving muscle of the chest wall can occur as a discrete mass or as diffuse tumor infiltration. Again, this may represent primary lymphoma, or more commonly, contiguous extension from an adjacent site.[93]

Malignant T-cell lymphoma of the skin, mycosis fungoides, manifests as erythema and eczema of the skin, progressing to indurated plaques with lymphadenopathy, finally progressing to ulcerated skin lesions. Advanced malignant T-cell lymphoma involves abdominal viscera, and has a very poor prognosis.[93]

Patients with chest wall lymphoma present most commonly in their sixth decade of life, and may have immunosuppression, associated with solid organ transplantation or AIDS. Lesions may infiltrate along neurovascular bundles and extend into subcutaneous tissues. On CT imaging, tumors have similar attenuation to muscle, with slight contrast enhancement. On T1-weighted MRI, lymphomas have signal intensity slightly less than muscle, and high signal intensity on T2-weighted MRI.[35]

Treatment of primary lymphoma of the bone is resection, with radiation therapy for positive margins. However, treatment is stage-dependent, and chemotherapy is the mainstay of treatment as most lymphoma presents in advanced stage.

### SOLITARY MYELOMA (PLASMACYTOMA)

Myeloma of the chest wall constitutes approximately 3 percent of malignant chest wall tumors.[3] The plasma cell tumor myeloma can develop either as a solitary lesion (plasmacytoma) or with a diffuse bone marrow infiltrate as multiple myeloma. In addition, solitary myeloma can progress to multiple myeloma. Solitary myeloma, which may present as a multicystic boney mass, or as an extraosseous lesion, typically presents in the sixth decade of life. Extraosseous solitary myeloma less commonly progresses to multiple myeloma. Both can occur in the chest wall, with osseous solitary myeloma more frequently involving the breast.

Chest wall myeloma typically appears as a lytic lesion on chest radiography. On T1-weighted MRI, myelomas have low signal intensity and high signal intensity on T2-weighted MRI.[35]

For biopsy-proven solitary lesions confined to the chest, radiation therapy can be employed for local control. Surgical resection can augment this should local control be difficult to achieve. In a large series of solitary myelomas, 69 percent 10-year survival was reported following treatment. However, there was an 85 percent local recurrence rate and 58 percent of patients progressed to multiple myeloma over 10 years.[94]

## COMMON METASTASES TO, OR INVASION OF, THE CHEST WALL

Overall, most patients who present with tumors involving the chest wall have local invasion of, or metastases to, the chest wall from nonprimary chest wall tumors. Several malignancies have a predilection to metastasize to the chest wall, or to invade it via growth from adjacent structures. These include lung cancer, breast cancer, melanoma, mesothelioma, lymphoma, and renal cell carcinoma. Lung cancer, of which approximately 5 percent undergoing resection have chest wall invasion, and mesothelioma are discussed elsewhere in-depth.

When considering surgical management for metastases to the chest wall, one must consider the role of resection for control of local symptoms versus curative intent. Each patient should be evaluated individually, including consideration of local control, prognosis, and quality of life following chest wall resection. We advocate surgical management when definitive local control has been achieved and there is no evidence of further metastases.

## SUMMARY

Chest wall tumors are rare, constituting a small portion of thoracic tumors. They include primary malignant and benign lesions, as well as metastases and locally invasive neoplasms.

Patient presentations vary, with most presenting with a painful mass, dyspnea, or other symptoms but one-quarter presenting with a painless, incidentally found lesion. Diagnosis rests on a combination of history, physical examination, axial imaging, and tissue biopsy.

Treatment is largely wide resection, with nuances in magnitude of resection, margins, and use of neoadjuvant and adjuvant chemotherapy and radiation therapy, based on diagnosis.

Resection may create a tissue defect in the chest wall, a dynamic structure. Therefore, reconstruction following resection may be simple or complex and involve tissue rearrangement or use of prosthetics.

The diagnosis and management of tumors of the chest wall remains a challenge for the thoracic surgeon. The engagement of a multidisciplinary team approach to diagnosis and management, including experienced assistance in the operating room, will lead to improved care and outcomes for patients with chest wall tumors.

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## CHEST WALL TUMORS BOARD REVIEW QUESTIONS (CHAPTER 18)

1. A 76-year-old man presents with a gradually enlarging mass involving the costochondral arch of his ninth rib anteriorly; core-needle biopsy is inconclusive. Which of the following statements is correct?

   A. Evidence of invasion indicates this is a chondrosarcoma.
   B. Homogeneous signal intensity on T1-weighted MRI indicates this is fibrous dysplasia.
   C. Lack of calcifications indicates this is an osteosarcoma.
   D. Heterogeneous appearance indicates this is a benign localized solitary fibrous tumor.

2. An 11-year-old boy presents with a tender left eighth rib lesion after being hit by a baseball. On CT imaging, this lesion has an amorphous calcified appearance. Which of the following does this most likely represent?
   A. Fibrous dysplasia
   B. Giant cell tumor
   C. Neurofibroma
   D. Rhabdomyosarcoma

3. Biopsy of a chest wall mass in a 63-year-old woman is consistent with diffuse B-cell lymphoma. Complete workup fails to identify any other sites of disease. Which is the correct treatment plan?
   A. Chemotherapy with cytoxan, adriamycin, vincristine, and prednisone.
   B. External beam radiation therapy
   C. Observation
   D. Surgical resection with radiation therapy for positive margins

4. Which of the following is the most common chest wall sarcoma in adults?
   A. Angiosarcoma
   B. Chondrosarcoma
   C. Ewing's sarcoma
   D. Osteosarcoma
   E. Rhabdomyosarcoma

5. A 6-year-old boy presents with a 3-cm, tender, right fourth rib mass. The lesion has an onion peel appearance on chest radiography. Which of the following does this most likely represent?
   A. Ewing's sarcoma
   B. Multifocal Langerhans cell histiocytosis
   C. Neuroblastoma
   D. Rhabdomyosarcoma
   E. Schwannoma

## ANSWERS

1. **Answer: A.** Evidence of invasion differentiates this as a chondrosarcoma as opposed to a chondroma. Fibrous dysplasia has a heterogeneous signal on T1-weighted MRI. Osteosarcomas are calcified. Benign localized solitary fibrous tumors have a homogeneous appearance on CT imaging.
2. **Answer: A.** Fibrous dysplasia is the most common benign rib lesion in children and has an amorphous calcified appearance on chest CT. Although giant cell tumors of the rib can occur in children, these are characterized by cortical thinning and rib disruption on CT imaging. Neurofibromas typically present in adults in their 30s and 40s. Rhabdomyosarcomas are the second most common malignant chest wall tumor in children, but lack calcifications on CT and MRI.
3. **Answer: D.** Primary lymphomas of the chest wall with no evidence of metastatic disease are managed by surgical resection with radiation therapy for positive margins. Chemotherapy (CHOP protocol) is reserved for systemic lymphoma. External beam radiation alone and observation are inappropriate management strategies.
4. **Answer: B.** Chondrosarcoma is the most common chest wall sarcoma in adults, followed by osteosarcoma. Angiosarcoma is rare, representing only 4 percent of adult chest wall sarcomas. Ewing's sarcoma is the most common malignant rib lesion in children, followed by rhabdomyosarcoma.
5. **Answer: A.** Ewing's sarcoma of the chest wall has a characteristic onion peel appearance on chest radiography. Multifocal Langerhans cell histiocytosis of the ribs is extremely rare. Neuroblastomas occur more commonly in infants than children. Rhabdomyosarcomas and schwannomas lack calcifications on imaging.

# 19 Congenital Chest Wall Anomalies

*Ibrahim Sultan*
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## KEY CONCEPTS

- Epidemiology
  - Pectus excavatum occurs in about 1:400 live births, with a male predominance of up to 5:1. No genetic abnormalities or chromosomal aberrations have been associated with pectus excavatum, although a familial tendency has been described. Up to two-thirds of children with Marfan's syndrome and a large proportion of Ehlers–Danlos patients develop pectus excavatum deformities. The incidence of pectus carinatum is about one-tenth that of pectus excavatum, with a similar male predominance and 25 to 30 percent reported family history. Scoliosis and other spinal deformities or a family history of these are associated with pectus carinatum.
- Pathophysiology
  - Pectus excavatum is a concave depression of the sternum resulting from abnormal growth, lengthening, rotation, or increased elasticity of the costal cartilages. Reduced cardiovascular performance has been linked to this defect. Pectus carinatum results from anterior displacement of the costal cartilages due to rotation and lengthening, leading to sternal protrusion. No significant cardiopulmonary abnormalities have been demonstrated with this lesion.
- Clinical features
  - In pectus excavatum, the sternum is posteriorly retracted and differential growth of the costal cartilages often results in an asymmetric chest wall with a common right-sided rotation of the sternum and an elevated left side. Other characteristic findings include sloped ribs, rounded shoulders with a classic stooped posture, and a protuberant abdomen. It is most commonly discovered in the first few years of life. Decreased stamina and endurance during exercise and excessive tachycardia/palpitations are commonly observed with this disorder. Pain is occasionally associated with this defect. Pectus carinatum is associated with pain, respiratory symptoms, ease of injury, and psychosocial body image concerns.
- Diagnostics
  - The best radiographic imaging modality for pectus deformities is the computed tomographic scan of the chest, which provides precise information regarding cardiac displacement, lung volumes, the degree of deformity, and any associated malformations.
- Treatment
  - Surgical correction of pectus excavatum includes the modified Ravitch repair (subperichondrial resection of all abnormal costal cartilages and wedge osteotomy to correct the posterior depression of the sternum by bringing it to a more anterior and neutral position) and the Nuss repair (using a precurved substernal bar to bend the sternum and cartilages to a corrected position). Surgical correction for pectus carinatum utilizes the basic principles employed in the open Ravitch repair, namely excision of all abnormal cartilages and return of the sternum to a neutral straight position.
- Outcomes/prognosis
  - The modified Ravitch or Nuss repairs represent the "gold standard" corrective operation for pectus excavatum. Hospitalization rarely exceeds 3 days, and 97 percent of patients experience a good result from the operation. Similar success rates are reported for Ravitch-type repairs of pectus carinatum. Complications include recurrence, pneumothorax, wound infection, atelectasis, and local tissue necrosis.

## INTRODUCTION

Children with congenital chest wall anomalies present from infancy to adolescence with cosmetic, psychological, or physiologic concerns. The spectrum of major anomalies of the chest wall includes pectus excavatum, pectus carinatum, Poland's syndrome, sternal clefts, and Jeune's syndrome.[1,2] The most common anomaly, pectus excavatum, is a concave depression of the sternum that comprises of majority of referrals seen by a pediatric surgeon for chest wall defects. Genetic or chromosomal associations with chest wall deformities are rare and include connective tissue disorders such as Marfan's and Ehlers–Danlos syndromes.[3,4] This chapter reviews the embryology of chest wall development as well as the pathophysiology, diagnosis, and treatment of the various congenital chest wall anomalies.

## HISTORICAL HIGHLIGHTS

The first reported repair of the pectus excavatum deformity, by Meyer, occurred in 1911.[5] Several reviews followed, but the benchmark repair, including costal cartilage excision and sternal osteotomy, was described by Ravitch in 1949 and has undergone only minor modifications in over 50 years of use.[6] Recently, experience has been growing with a minimally invasive technique for pectus excavatum repair described in 1998 by Donald Nuss.[7] Ravitch is also credited with the first repair of a pectus carinatum defect in 1952.[8] Jeune and colleagues described the syndrome of asphyxiating thoracic dystrophy in 1954,[9] and Cantrell, in 1958, described the pentalogy that includes lower sternal clefts.[10]

## EMBRYOLOGY

The chest wall consists of muscles derived from myotomes and ribs, costal cartilages, and components of the sternum from the axial skeleton. Shortly after the fifth week of development, dermomyotomes in the thoracic region split and form myotomes, from which the chest wall musculature arises. The mesenchymal costal processes of the developing thoracic vertebrae give rise to the ribs starting at week 5 after fertilization.[11,12] During the embryonic period, the costal processes become cartilaginous and finally undergo endochondral ossification to become ribs. The synovial costovertebral joints arise from the embryonic junction between the vertebrae and the costal processes. During week 6 of development, a pair of vertical mesenchymal structures, known as sternal bars, develops ventrolaterally along the body wall. These bars gradually fuse craniocaudally in the median plane as they chondrify to form precursors of the manubrium, sternebral segments of the sternal body, and xiphoid process. Ossification of the sternum also occurs in a craniocaudal fashion and is complete by 60 days postfertilization except for the xiphoid, which ossifies after birth. Incomplete sternal fusion is not uncommon and can lead to bifid xiphoid or a spectrum of sternal clefts.

## PECTUS EXCAVATUM

Abnormal growth, lengthening, rotation, or increased elasticity of the costal cartilages leads to the relatively common depression of the sternum known as pectus excavatum. Clinical findings usually begin to manifest by 2 to 3 years of age, but—given the risk of acquired thoracic dystrophy or recurrence after correction in younger patients—operative intervention should occur in older children or adolescents. The physiologic benefit of pectus excavatum repair is frequently discussed but remains controversial and is based mostly on retrospective data. Two repairs are most commonly performed, an open repair, first described by Ravitch, and a less invasive bar repair, described by Nuss. The type of repair is chosen based on the surgeon's experience and the complexity of the deformity. Both techniques have demonstrated good results when the appropriate patient is selected at the appropriate age for repair. The latter approach described by Nuss has become more popular in many centers across the world. These patients are not only referred for the Nuss procedure by primary care physicians, but majority of such patients are self-referred because of information available on the World Wide Web.[13]

## DEVELOPMENT

There is no known cause for pectus excavatum. Cartilaginous growth appears to be abnormal, which causes either posterior depression of the sternum in the case of abnormal lengthening of the cartilages or rotation of the sternum in the case of differential cartilaginous growth. The sternum itself does not appear to play a causative role in excavatum or carinatum. A study of the biomechanical, morphologic, and histochemical properties of cartilage from children with pectus excavatum shows decreased tension, compression, and flexure, with disrupted type II collage patterns in the deep zones of the cartilage.[14]

## EPIDEMIOLOGY

Pectus excavatum is relatively common, occurring in approximately 1:400 live births, with a male predominance of up to 5:1.[15] No genetic abnormalities or chromosomal aberrations have been associated with pectus excavatum, although a familial tendency has been described.[15,16] Up to two-thirds of children with Marfan's syndrome and a high frequency of Ehlers–Danlos patients develop pectus excavatum deformities.[3,4] Children with connective tissue disorders can present later in life, have more progressive defects, and suffer from

more complicated postoperative courses, but successful cosmetic and functional results can be achieved even in these patients.[4] Other associations include cardiac disorders[17] and scoliosis.[18]

## PATHOPHYSIOLOGY

Pediatric surgeons performing pectus excavatum repair argue that children with pectus excavatum seem to enjoy an increase in stamina and cardiovascular performance after surgical correction. However, it is unclear whether the cardiopulmonary advantages are conferred on these patients after undergoing repair of their pectus excavatum. These advantages quoted in the literature are mostly based on retrospective data.[19,20]

Two organ systems have been examined for physiologic differences in pectus excavatum: pulmonary and cardiovascular. Static pulmonary function tests performed at rest seem to show few abnormalities in children with pectus.[21,22] Other studies have confirmed the lack of difference in static lung volumes and baseline resting pulmonary function before and after both Ravitch and Nuss repairs,[23,24] while some even argue for a possible worsening of lung function after chest wall reconstruction.[25–28] In reviewing these studies, the majority of children are at the lower end of the "normal range" of pulmonary function, suggesting a defect. Interestingly, decreased postoperative pulmonary function testing in some studies has been found in contrast to subjective improvement in exercise stamina.[27] In some studies, including those that show no difference in resting pulmonary tests, exercise pulmonary function shows significant differences in lung volumes in preteen and teenaged pectus patients.[21,29] A recent study by Haller and coworkers shows a lower forced vital capacity (FVC) in pectus patients before surgery, with over half complaining of exercise limitation; significant improvement was found in 66 percent of these patients after repair.[30] Patients with abnormal ventilation/perfusion scintigraphy scans have demonstrated improvement after surgical correction of pectus deformity.[31] Although vital capacities were reported as only mildly reduced or normal in pectus patients, a nonlinear increase in oxygen uptake was seen when compared with controls, possibly indicating an abnormal work of breathing during exercise.[32] In another study, all pectus patients experienced improvement in maximal voluntary ventilation and exercise tolerance.[33] Some authors believe that the improvement of pulmonary function after pectus repair can be appreciated only in children who have severe deficits preoperatively.[34]

Reduced cardiovascular performance, rather than ventilatory limitations, has been the focus of a number of studies in an effort to understand the physiologic manifestations of pectus excavatum.[35,36] Right ventricular filling seems to be diminished with this condition and somewhat alleviated after repair.[37] Kowalewski and colleagues showed increased right ventricular systolic, diastolic, and stroke volumes after surgical correction of pectus excavatum.[38] A lower heart rate and expanded cardiac stroke volume have been described after pectus repair,[27,28,33] as has a higher oxygen pulse and cardiac output.[29,30] For this reason, routine cardiology evaluation in patients with known rhythm abnormalities, right atrial and ventricular hypertension, and mitral valve prolapse is prudent. Studies have indicated a significantly higher proportion of patients with mitral valve prolapse in patients with pectus excavatum when compared with control children in the same age group.[13]

In addition to the apparent cardiopulmonary advantages of pectus repair, the psychological and psychosomatic aspects associated with this disease cannot be underestimated. School-aged children with pectus excavatum suffer from embarrassment, social anxiety, orientation toward failure, marked depressive reactions, feelings of stigmata, reduced tolerance of frustration, and limited capacity for work.[39] In many children, these body image issues alone merit surgical intervention; when combined with the apparent cardiopulmonary advantages of correction, these considerations should clearly urge all health care providers to be supporters and advocates of treatment of pectus excavatum.

## CLINICAL FEATURES

Figure 19-1 illustrates the classic physical features of a child with pectus excavatum. Most children who present for surgical evaluation are active and healthy-appearing, with the chief complaint of a visible anatomic defect. Several relatively younger patients may also present to the office with their parents who clearly recognize the anatomic defect but is not obvious to the child. Physical examination of such children may demonstrate sloped ribs, rounded shoulders with a classic stooped posture, and a protuberant abdomen. When the excavatum defect is severe, the cardiac point of maximal impact can be shifted laterally beyond the midclavicular line. Pectus excavatum is most commonly discovered in the first few years of life, although it can be apparent in the newborn period or in a delayed fashion later in development. In newborns, pectus excavatum can be associated with paradoxical chest wall movement with ventilation. Although pectus excavatum may present at birth, most patients present after prepubertal spurt. These are typically boys in majority of the case. 20 to 30 percent of such patients may have accompanying scoliosis. Marfarnoid features may be seen in up to 20 percent of such patients.[13] Many of these anomalies can resolve spontaneously during the early years and should not be considered for surgical repair until ages 8 to 12.

Physically active children often complain of shortness of breath during exercise or decreased exercise tolerance when compared with their peers, but they generally have no symptoms at rest. Excessive tachycardia or palpitations during mild exercise can also be seen in patients with this disorder.[15] In a 30-year review of 375 patients undergoing pectus repair, 67 percent reported preoperative decreased stamina and endurance during exercise, 32 percent had frequent respiratory infections, 8 percent had chest pain, and 7 percent had

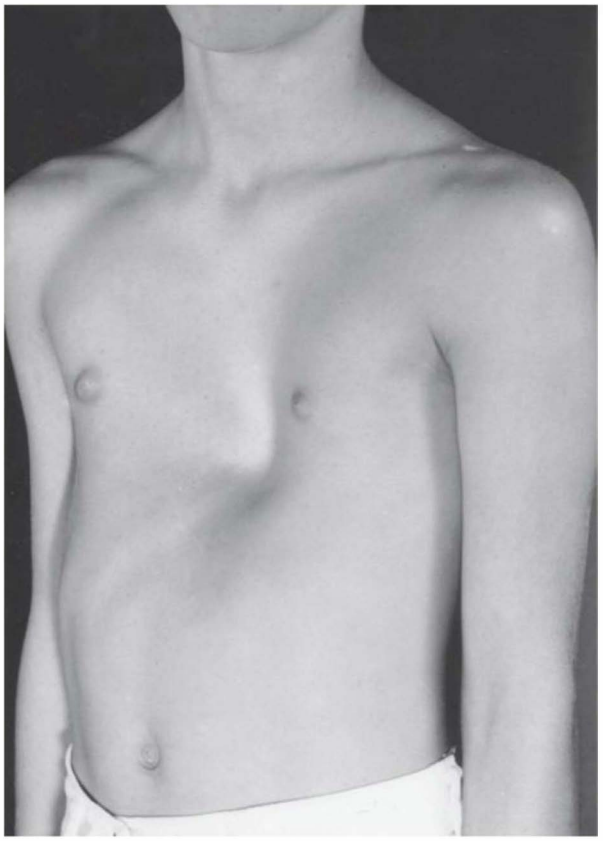


FIGURE 19-1 Child with pectus excavatum. Note the rounded shoulders, central defect, and "pot belly."

asthma.[40] Another 30-year study found, at initial presentation, 56 percent of subjects with dyspnea on exertion, 29 percent with shortness of breath at rest, 10 percent with chest pain, and 10 percent with palpitations.[41] Table 19-1 summarizes the signs and symptoms of pectus excavatum.

**TABLE 19-1: Signs and Symptoms of Pectus Excavatum**

| |
|---|
| Physical signs |
| Visible depression of lower sternum |
| Right-sided rotation of sternum with asymmetrical chest wall |
| Sloped ribs |
| Rounded shoulders |
| Protuberant abdomen |
| Laterally displaced cardiac point of maximal impact |
| Associated findings of connective tissue disorders |
| Symptoms |
| Nonspecific parasternal chest pain |
| Decreased subjective exercise tolerance, work capacity |
| Frequent respiratory infections, exercise-induced asthma |
| Embarrassment reactions, social anxiety, depression, suicidal thoughts |

## IMAGING STUDIES

Many centers will begin the workup with a preoperative chest radiograph. Apart from being readily available and inexpensive, it allows measurement of severity index. In children with recurrent pectus excavatum, it helps detect the extent of abnormal calcification of cartilages. Regardless of the surgical approach selected, the best radiographic test for preoperative evaluation of a patient with pectus excavatum is computed tomography (CT) of the chest.[42–44] This study provides precise information regarding cardiac displacement, lung volume, and, most importantly, the most accurate measurement of the depth of the sternal defect and its relationship to the overall width of the thorax.[45] The Haller index can be obtained by measuring the ratio of the AP distance between the vertebral bodies and the sternum at its narrowest point and the transverse diameter of the chest. This can be performed on physical exam or more reliably by a CT scan. Although age and gender-related variability exists in the Haller index,[46] normal children should not have a Haller index greater than 2.5, while the severity index of those with pectus excavatum generally ranges from 3 to 6 (Figs. 19-2 and 19-3A and B). Magnetic resonance imaging (MRI) has been used in patients where radiation exposure is a concern, particularly in those children that are cooperative and do not need sedation or general anesthesia for MRI.

## INDICATIONS FOR OPERATION

Factors determining candidates for repair of pectus excavatum defects include anatomic, physiologic, psychological, considerations as well as proper timing (Table 19-2). A CT scan can accurately define the anatomic defect, including the severity index of the sternal depression as well as its effects on cardiac and pulmonary anatomy. A Haller index of 3 or greater is associated with the presence of pectus excavatum.

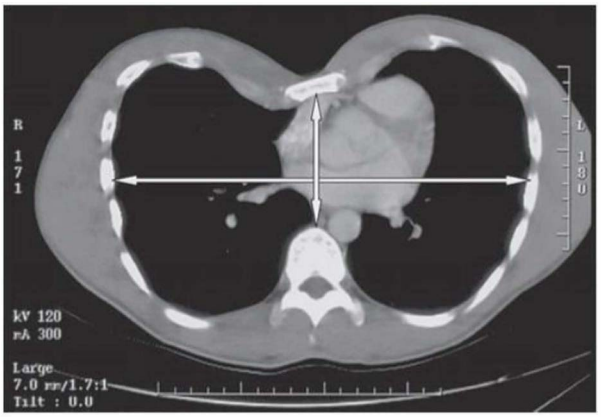



FIGURE 19-2 Cross-sectional CT scan to measure the Haller index. CT scan taken at the deepest part of defect. The Haller index is equal to the transverse diameter of the thorax divided by the anteroposterior dimension.

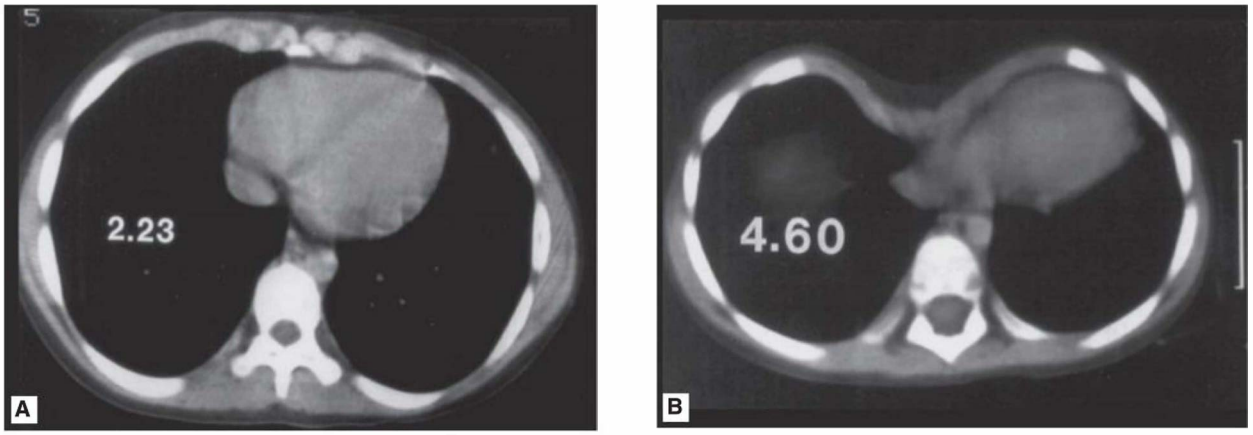



**FIGURE 19-3** **A.** Chest CT scan of a normal child. The Haller index should be <2.5. **B.** Chest CT scan of a patient with severe pectus excavatum.

All candidates should undergo stress pulmonary function studies and, if indicated by stress pulmonary function or history, echocardiography. Based on patient and family history—including double joints, joint dislocations, hyperflexibility, accelerated worsening of eyesight, and mitral valve prolapse—a screen should be considered for connective tissue disease. Associated chest pain, dyspnea on exertion, decreased exercise tolerance, exercise-induced asthma, or cardiac anomalies are possible indications for operative correction.[27,28,33–36] Patients who begin with symptoms such as dyspnea on exertion or exercise-induced chest pain show significant improvement of these symptoms postoperatively.[40,47] In addition, the need for future sternotomy, as in children with Marfan's syndrome, should be considered an indication for correction in childhood.[48]

Psychological symptoms are not uncommon in these patients and include embarrassment reactions, marked depressive reactions, social anxiety, feelings of stigmata, and others.[39] These manifestations can seriously alter the mental and physical health of a child and should be strongly considered in deciding candidacy for operative repair.

Proper timing of surgical repair is essential for adequate outcome, although this is also frequently debated and based on retrospective data. In general, good results have been reported with correction in school-aged children between the ages of 8 and 16, either before or after but not during their pubertal growth spurts.[15,42,49] The advantage of undergoing a repair before puberty is the ability of the bar to stabilize the malleable chest during this period and throughout the puberty spurt. This in turn leads to shorted recovery time and low incidence of recurrence.[48] It remains clear that Ravitch repair in patients younger than 7 years of age should be avoided because of a higher incidence of damage to the cartilaginous growth centers, with resulting acquired Jeune's syndrome.[30,50–53] A Nuss repair in patients around 8 years of age is sometimes justified when they have significant cardiopulmonary compression from their defect. In such situations, the bar should be left for up to 3 years. Additionally, the parents should appreciate that there is a higher risk of recurrent pectus excavatum when repaired at this age. The reason for higher recurrence in this age group is the removal of bar prior to pubertal growth spurt. Timing should vary with indication, as with the example of lower incidence of recurrence in children with Marfan's syndrome who underwent repair after maximal growth was obtained.[54] Success has been reported with simultaneous correction of pectus excavatum and congenital cardiac defects.[55] Age should not be a barrier to repair, as excellent long-term cosmetic results and symptomatic relief approaching 90 percent have been described in adults between the ages of 16 and 68 years.[41]

**TABLE 19-2: Indications for Surgical Repair of Pectus Excavatum Deformities**

| |
|---|
| Cardiorespiratory symptoms |
| Exercise intolerance |
| Abnormal pulmonary function testing |
| Abnormal echocardiogram |
| Exercise-induced asthma |
| Body image issues |
| Anatomic severity |
| Haller index >3.0 |
| External measurement >2.5 |

## MODIFIED RAVITCH REPAIR

Almost 60 years ago and for several decades to follow, Ravitch described subperichondrial resection of the lower costal cartilages with wedge osteotomy of the sternum as a possible repair for pectus excavatum.[6,56,57–60] This has gained wide acceptance as the gold standard operation for pectus excavatum, especially for complex or recurrent cases. Extensive experience has been reported with this procedure, and outcomes are generally excellent.[42,44,61–66] One group has reported some success with a minimally invasive endoscopic Ravitch repair.[67]

**TABLE 19-3: Summary of Operative Steps in the Modified Ravitch Repair for Pectus Excavatum**

| |
|---|
| Incision (midline or transverse) through the depth of the defect |
| Skin and muscle flaps to expose sternum and costal cartilages |
| Subperichondrial cartilage resections, usually four bilaterally |
| Sternal mobilization and transverse osteotomy |
| Sternal support; cartilage tripod and retrosternal bar |
| Wound closure with retrosternal chest tube, subcutaneous drain |

## Incision and Exposure

A modified Ravitch repair as performed at Johns Hopkins Hospital has been described (Table 19-3). A transverse inframammary skin incision is utilized at the level of the deepest portion of the sternal defect. Usually cosmetic outcomes from transverse incisions for this operation are more appealing than vertical ones. Upper and lower skin flaps are created in the subcutaneous layer, followed by creation of midline muscle flaps elevating the pectoralis muscles. This exposes the costal cartilages in their entire length bilaterally along the affected portion of the sternum. In most cases, this includes the fourth through seventh cartilages, but it can include as high as the second and third in severe cases of pectus excavatum. Exposure of the upper flap should extend to at least one normal cartilage cranial to the uppermost abnormal one, with the goal of excising at least four cartilages bilaterally.

## Subperichondrial Resection

One of the two principal goals of the operation is subperichondrial resection of all abnormal costal cartilages (Fig. 19-4A). These are resected from the lateral point of union with the rib, extending medially to the chrondrosternal junction. To keep the resection subperichondrial, the perichondrium is incised anteriorly along each cartilage, and upper and lower flaps of perichondrium are created to expose the deformed cartilage. It is imperative to keep the perichondrium entirely intact and not devascularized, as this

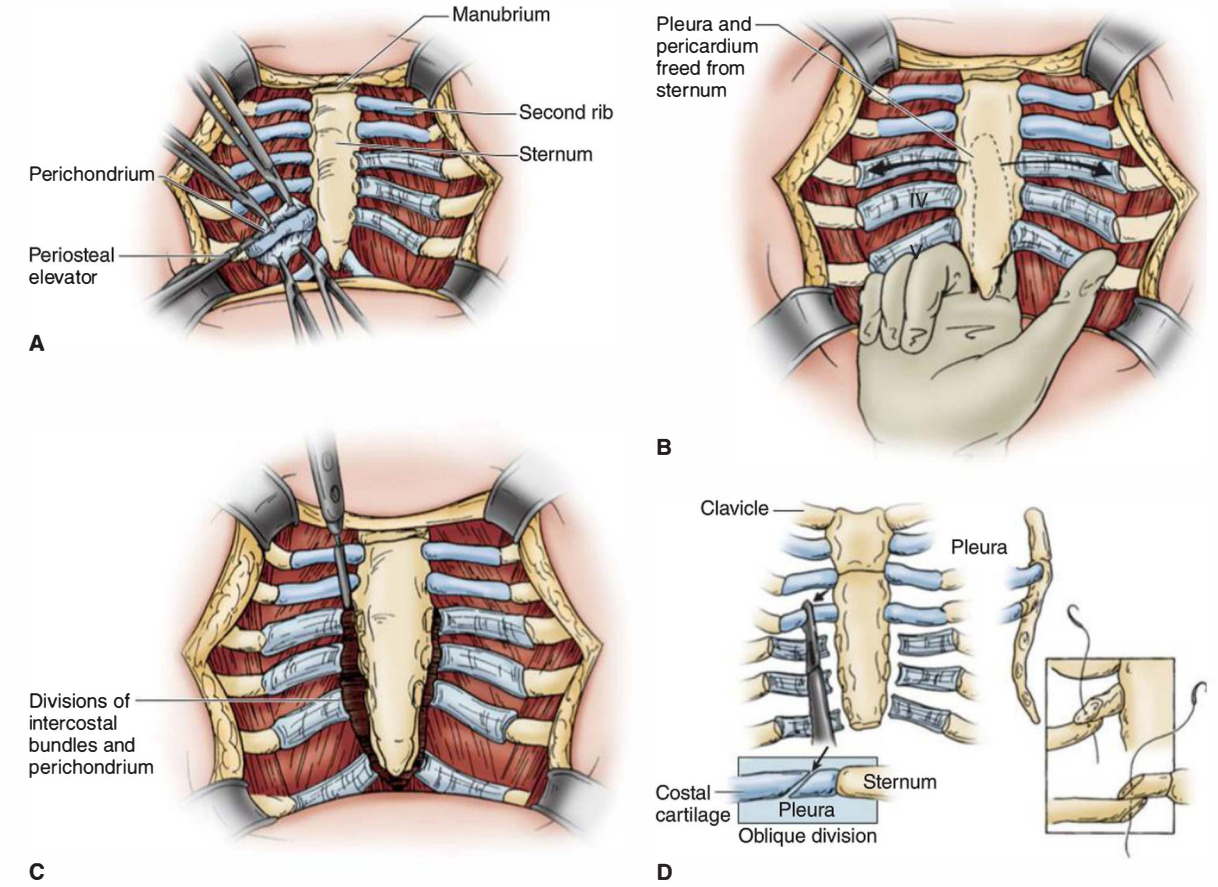



**FIGURE 19-4** Summary of the modified Ravitch procedure. **A.** Exposure of the anterior chest wall and excision of four costal cartilages bilaterally. **B.** Elevation of the sternum and its freeing from the underlying pleura (pericardium). **C.** Division of intercostal bundles. **D.** Oblique chondrotomy of three cartilages to form tripod.

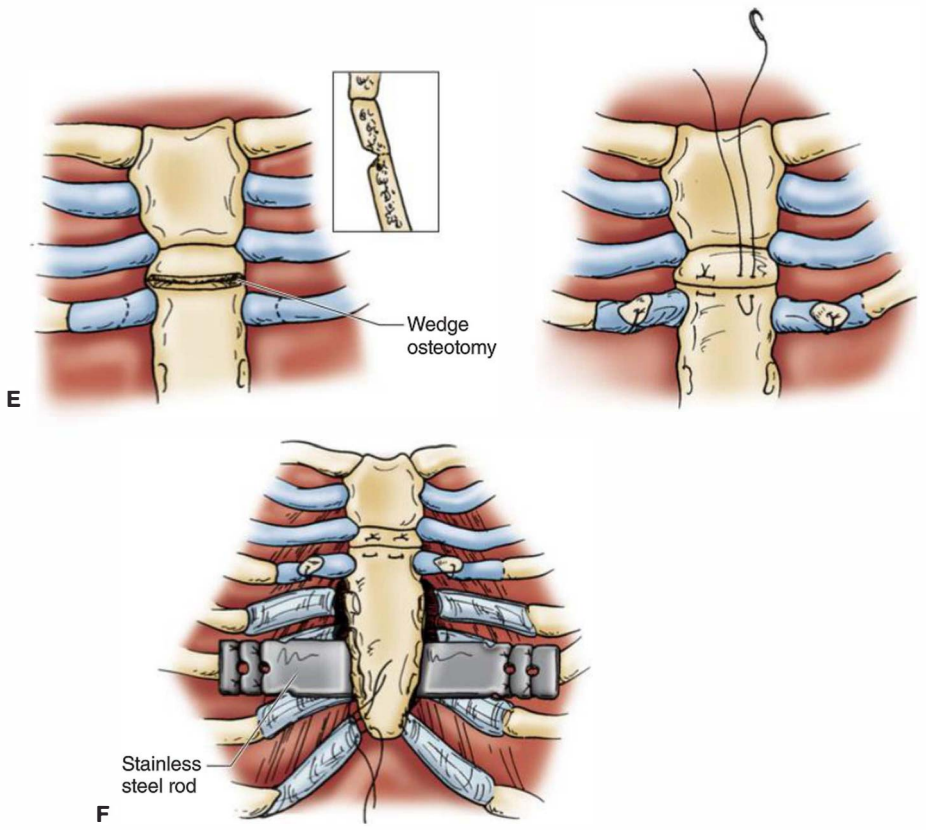



**FIGURE 19-4** (*Continued*) **E.** Transverse osteotomy. **F.** Placement of substernal strut.

provides the basis for new cartilage growth and subsequent bone. It is also suspected that devascularization of the perichondrium can contribute to the acquired Jeune's syndrome. During the dissection of the posterior perichondrium, care must be taken to avoid violating the pleural space.

## Wedge Osteotomy

The xiphoid is exposed and elevated, allowing for the creation of a substernal plane (Fig. 19-4B). This is performed mostly by blunt dissection, taking meticulous care to preserve the pleura and the pericardium as it is swept from the posterior surface of the sternum. The perichondrial bundles at the level of all of the excised cartilages are detached from the sternum, making sure that the internal mammary artery is swept laterally with the intercostals bundle and perichondrium. Just above the resected cartilages, the wedge osteotomy is performed (Fig. 19-4C). This is an anterior, triangular incision in the anterior table of the sternum performed to correct the posterior depression of the sternum by bringing it to a more anterior and neutral position. A single osteotomy is usually performed between the second and third cartilages, although at times a second osteotomy can be performed in a more caudal location (Fig. 19-4D). Tripod supports consisting of the lowest third or fourth intact costal cartilages can be used to support the sternum as well by obliquely dividing them in a medial-to-lateral trajectory and then placing the medial portion atop the lateral. Finally, for further security, the sternal periosteum is sutured in the position fashioned during the operation (Fig. 19-4E).

## Support Bar

Various modalities have been described to further support the sternum after wedge osteotomy. Autologous perichondrium has been used,[68] as have various metal struts with or without synthetic envelopes.[69] We prefer selective use of stabilizing struts for patients over the age of 10 or 12 or those with connective tissue diseases such as Marfan's or Ehlers–Danlos syndrome. A substernal stainless steel bar can be placed under the distal third of the sternum and secured in place laterally to the medial aspect of surrounding ribs (Figs. 19-4F and 5A and B). Interrupted sutures are generally sufficient to secure the bar. Alternatively, sternal fixation bars, which need to be sized and bent to configure to the contour of the sternum, can be screwed in place (Fig. 19-6A and B).

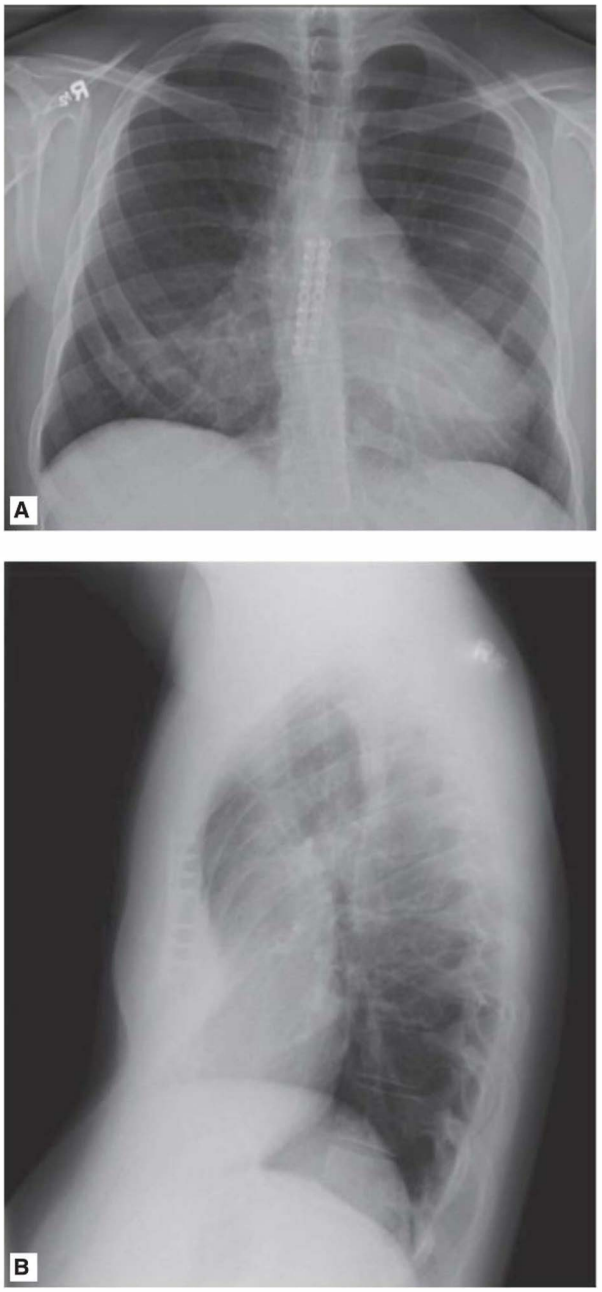



**FIGURE 19-5** PA (**A**) and lateral (**B**) chest x-ray of sternal fixation bars in place after wedge osteotomy. Screws are inserted above and below the osteotomy site (where there are no screws in the plate).

## Postoperative Management

It is not necessary to suture intercostal bundles that have been detached from the sternum back into place. If this defect is small, however, it can be closed by approximating nearby tissues. Retrosternal and subcutaneous chest drains are placed and can be removed 2 to 3 days postoperatively. After drains are removed, oral analgesia is sufficient and patients can be discharged within 3 to 4 postoperative days. A bladder catheter is recommended for the first day or two in the teenager and older patient, in whom urinary retention is not uncommon. Incentive spirometry is critical to prevent atelectasis. Contact sports for 6 to 8 weeks are usually avoided to allow cartilage regrowth and sternal fixation. A support bar, if placed, should remain for at least 6 months and can be removed in an outpatient procedure.

## Outcomes and Complications

For almost six decades, thousands of patients with pectus excavatum have been successfully treated with some modification of the Ravitch repair and followed for significantly long periods of time.[15,24,40–42,44,47,63,65,70–77] This is the gold standard operation to which all new techniques are compared.

The psychological benefits of the operation are clear.[39] The physiologic benefits of pectus repair remain controversial, with some groups demonstrating a measurable physiologic advantage[21,27–33,37] and others showing no difference before and after corrective operations.[23–28] It is possible that only selected patients with certain preoperative physiologic handicaps will benefit in this regard from surgical repair.

Hospitalization rarely exceeds 3 days, and 97 percent of patients experience a good result from the operation.[15] Although the operation is mostly performed in male patients, females with pectus deformities fare equally well after surgical repair.[70] Complications generally occur in fewer than 5 percent of patients undergoing a modified Ravitch repair; these are listed in Table 19-4. Early complications include pneumothorax, pleural effusion, pericarditis, seroma, wound infection, urinary retention, and atelectasis. Bar migration and pectus recurrence can occur as late complications. Acquired Jeune's syndrome is a terrible complication and is discussed later in this chapter. Urinary retention is usually seen in older teenagers and

**TABLE 19-4: Complications Following Modified Ravitch Repair for Pectus Excavatum**

| |
|---|
| Early |
| Pneumothorax |
| Atelectasis |
| Pleural effusion |
| Pericarditis |
| Seroma |
| Wound infection |
| Urinary retention |
| Late |
| Bar migration |
| Recurrence |
| Acquired Jeune syndrome |
| Floating sternum |

adults and 1 to 2 days of bladder catheterization is required in this population. In addition, aggressive pulmonary toiled is advocated to reduce atelectasis and the risk of pneumonia. Recurrence occurs in approximately 2 percent of patients, with a higher incidence if the operation was performed at an early age (below 7 years).

In a review of 375 patients over 30 years, Fonkalsrud and associates report 12 cases of atelectasis, 13 pleural effusions, 5 recurrences, and 3 patients with pericarditis.[40] Of 777 procedures for pectus repair in a single center, 98.5 percent were successful, with an overall complication rate of 6.7 percent, a major recurrence rate of 1.5 percent, and a minor recurrence rate of 4.5 percent.[73] Shamberger and coworkers reported 704 patients seen over a period of 30 years who were repaired by a modified Ravitch technique, with 4.4 percent rate of complications including 11 cases of pneumothorax, 5 wound infections, 1 seroma, 1 hemopericardium, and 17 major recurrences (2.7 percent), of which 12 required revision.[44]

Complications may occur more commonly in adults because of the magnitude of dissection required and the anatomic difference that cartilage has developed into bone. Still, this operation is safe and successful in adults, with no statistical significance in reported complications in most studies. Of 116 patients over the age of 18 undergoing modified Ravitch repair, Fonkalsrud and colleagues report 7 pleural effusions, 2 pneumothoraces, and 2 patients with pericarditis.[47] Table 19-4 summarizes complications of the Ravitch operation.

## NUSS REPAIR

In 1998, Nuss reported a seminal 10-year series of 42 patients for whom he achieved adequate correction of pectus excavatum defects using a minimally invasive approach that does not involve excision of the costal cartilages.[7] Instead, through small bilateral incisions, a convex steel bar was surgically placed under the sternum to allow repositioning and remodeling of the deformed costal cartilages and sternum. After keeping the bar in place for 2 years to allow distraction and splinting of the costal cartilages as well as rotation of the sternum to a more neutral position, the bar was removed. Although a number of modifications have been described, experience with this procedure has become extensive, outcomes remain excellent, and the modified Nuss procedure has become the initial procedure of choice for many pediatric surgeons.[78–82] Success has even been reported for this procedure in the repair of patients failing modified Ravitch procedures.[83]

### Positioning, Incision, and Exposure

The patient is positioned supine on the operating table with arms abducted at the shoulders (Fig. 19-6A). This allows access to the lateral chest wall for bilateral 5-cm transverse incisions positioned just above the deepest portion of the sternal defect. Care should be taken to avoid hyperabduction, thus resulting in possible brachial plexus injury. Alternatively, the patient's torso can be supported by a mattress and arms can be extended posteriorly. This is particularly advantageous when using a thoracoscope. The thoracoscope can be placed superior to the incision. However, the chest can be overextended with this position, thus altering the patient's anatomic deformity. Variations exist regarding ideal placement of the incisions and support bar. In our experience, placement of the incisions at the caudalmost portion of the defect within the costosternal region, avoiding the xiphoid, allows for optimal results in almost all types of patients. In addition, the older the patient, the more medially the bar should pass the chest wall. This provides for a shorter and thus stronger arch to elevate the sternum.

On both sides, flaps of skin and subcutaneous tissues are raised, using electrocautery to expose one intercostal space above and below the chosen incisions. This mobilization provides room for the laterally placed bar stabilizers. Using the intercostal space corresponding to the deepest portion of the sternal defect, the pleural space is entered bilaterally, protecting the lung from parenchymal injury during this maneuver. Usually the anterior axillary line is chosen as an entry point, allowing for entry where the ribs transition from the anterior to the lateral chest wall.

### Retrosternal Dissection

A retrosternal tunnel is next created to allow passage of the steel bar in the retrosternal space. A Crawford clamp or similar device is carefully advanced by blunt dissection from the left hemithorax to the right side. For this maneuver, bone hook elevation of the distal sternum or video-assisted thoracoscopic surgery (VATS) may be helpful or necessary. We insist that the clamp pass from left to right, thus avoiding injury to the heart and pericardium. An umbilical tape is attached to the clamp and pulled retrogradely back through the retrosternal tunnel (Fig. 19-6B–D).

### Lorenz Bar

Using a series of bar templates, the appropriate size and approximate shape are selected for the stainless steel Lorenz bar (Walter Lorenz Surgical, Jacksonville, FL) (Fig. 19-6C). With the help of a bar-bending system, the bar is curved so that the substernal segment is as flat as possible to afford a sturdy support. One of the umbilical tapes is tied to the end of the Lorenz bar, and it is guided with the concave side up (upside down) through the retrosternal tunnel from left to right using VATS or sternal elevation (Fig. 19-6D). A steel bar turner is used to flip the bar in a craniocaudal direction and hold it in place while the correction of the pectus defect is examined (Fig. 19-6E). To remain most stable, the lateral parts of both sides of the bar arch must rest on the rib cage. Major changes to the concavity of the bar may require

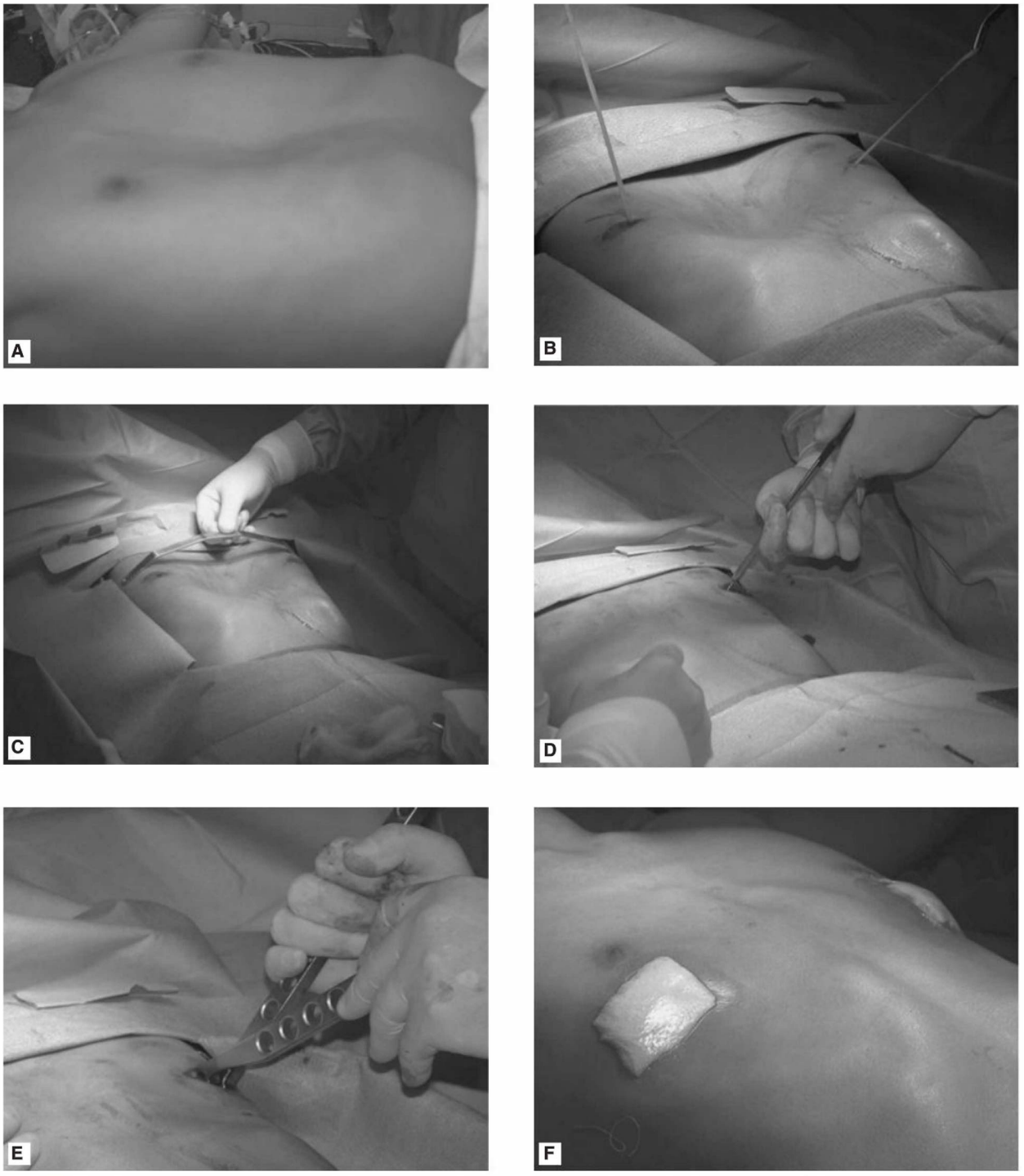



**FIGURE 19-6** Nuss repair. **A.** Patient positioned for procedure with arms outstretched. **B.** Umbilical tape is threaded through a retrosternal tunnel. **C.** Lorenz bar curved to conform to the patient's chest. **D.** After incisions are made into the pleural space bilaterally, a retrosternal tunnel is made and the bar is threaded through the tunnel, using the umbilical tape. **E.** Bar benders are used to bend the bar against the lateral chest wall. Stabilizing clips and stainless steel wires are used to further immobilize the bar. **F.** Completion of operation without chest tubes or drains.

**TABLE 19-5: Summary of Operative Steps in the Modified Nuss Repair for Pectus Excavatum**

1. Bilateral inframammary incisions at the deepest level of the sternum
2. Template measurements to determine length of bar; precurve bar to chest size
3. Development of retrostrenal plane from left to right (with or without thoracoscopy)
4. Passage of substernal clamp/umbilical tape
5. Insertion of pectus bar under sternum
6. Bar rotation and application of stabilizers
7. In situ bar bending and fixation with 5-mm or 6-mm surgical wire
8. Wound closure

unflipping the bar, with or without removal, and rebending it. Minor changes can be fixed with an in situ bar-bending system, which, in our experience, allows for optimal contour and subsequent stabilization. We place bilateral stabilizing clips and bend the end of the bar to keep the stabilizer in place. The bar is also fixed to the crossing rib using no. 5 or 6 wire sutures medial to each clip. Table 19-5 outlines these steps in the operative procedure.

## Evacuation of Pneumothorax

Usually, no chest tubes or drains are required (Fig. 19-6F). For closure, continuous fascial sutures are placed bilaterally but not tied. Then 40 cm of sustained inspiratory pressure is administered by the anesthesia team while the sutures are quickly pulled up and tied after the pleural air has escaped. Skin is reapproximated using a running subcuticular closure.

## VATS

Although VATS is not routinely used in the pediatric population, it is used at many centers performing the minimally invasive Nuss procedure. Typically right-sided VATS is used, but some surgeons employ either left-sided or occasionally bilateral approaches.[48,74] The trocar for VATS can be either inferior to the incision or through the incision site itself. The goal is to keep the introducer tip in view during VATS. If there is poor visualization from the ipsilateral side, the thoracoscope should be inserted from the contralateral side to visualize the introducer tip.

## Postoperative Management

Patients undergoing a modified Nuss procedure have a significant amount of postoperative pain; this is usually the limiting factor for discharge planning. In our experience, the analgesia requirement is even greater for this procedure than for the modified Ravitch repair. Patients should be placed on a patient-controlled analgesia (PCA) pump. Older patients are offered an epidural catheter. The PCA is discontinued within 48 to 72 h after which oral analgesics are used. Ketorolac is often added to the postoperative analgesic regimen. Patients are also prophylactically started on stool softeners to prevent constipation. Most patients are discharged on postoperative day 4 or 5. They are encouraged to return to school when they feel able to do so. This is usually 2 to 3 weeks after the operation. We restrict participation in sporting activities for up to 6 weeks. The Lorenz substernal bar is left in place for a period of at least 2 years to allow for optimal remodeling of the costal cartilages and repositioning of the sternum. Longer bar placement may be used for patients requiring reoperation and those with elastic cartilage abnormalities. Bar removal is usually an outpatient procedure and should not be scheduled during a growth spurt.

## Outcomes and Complications

The original report of 42 patients by Nuss and associates in 1998[7] has been followed by two reports from his group describing a 14-year experience of repair in 329 patients, including 14 reoperations for failed Ravitch repairs and 10 for failed Nuss repairs (2 of which were performed by the Nuss group).[78,82] Perioperative antibiotics and aggressive incentive spirometry are advocated to prevent bar infection, pneumonia, and atelectasis. Epidural anesthesia is recommended for analgesia, and both VATS and sternal elevation are described for bar insertion to minimize the risk of mediastinal injury. They report no cases of cardiac perforation, thoracic chondrodystrophy, or death using these techniques. Although 52 percent of patients developed pneumothorax, most resolved spontaneously, with only 1.2 percent requiring aspiration and 1.5 percent requiring tube thoracostomy. Pericarditis responsive to either indomethacin or pericardial fluid aspiration was reported in 2.4 percent of patients in this review, pneumonia in 0.9 percent, and wound infection in 2.6 percent, responsive mostly to antibiotics but resulting in bar removal in 3 patients. Before the routine use of bar stabilizers, bar displacement occurred in 15.7 percent of patients; this was reduced to 5.4 percent with stabilizers and even further with wire sutures. In 13 percent of these patients, double stabilizing bars were used.

Several other large series have reported similarly encouraging results, with good results in over 95 percent of patients but also with a reminder that a learning curve is associated with the introduction of this new technique.[79–81,84] Quality of life has been studied objectively and, using two quality-of-life models, was found to be improved.[85] Complications of the Nuss procedure include ileus, pleural effusions, atelectasis, flipped or displaced bar, pericarditis, chronic pain, worsening of chest wall asymmetry,[84] anterior thoracic artery pseudoaneurysm, thoracic outlet obstruction,[79] sternal erosion, and liver injury.[80]

**TABLE 19-6: Complications of Modified Nuss Procedure**

| |
|---|
| Early |
| Pneumothorax |
| Hemothorax |
| Cardiac or pulmonary parenchymal injury |
| Wound hematoma Bar movement/turning with recurrence |
| Wound infection |
| Rib fracture |
| Arrhythmias |
| Late |
| Bar movement |
| Chronic pain/neuropraxia |
| Erosion through sternum or rib |
| Wound infection |
| Recurrence |

A review of three major complications following Nuss repair was reported by Moss and colleagues.[86] One patient suffered a cardiac perforation requiring urgent sternotomy and repair on cardiopulmonary bypass. A second patient required open pleural and cardiac debridement for staphylococcal sepsis, bilateral empyema, and bacterial pericarditis. Three patients suffered thoracic outlet syndrome with persistent paresthesias. Postpericardiotomy syndrome refractory to nonsteroidal anti-inflammatory treatment has also been described and treated successfully with intravenous methylprednisolone. Table 19-6 outlines the complications reported following the modified Nuss procedure.

A recent meta-analysis that compared the Nuss and the Ravitch procedure found no significant differences in overall complications, length of hospital stay and time to ambulation. However, the rate of reoperation, postoperative hemothorax and pneumothorax after the Nuss procedure were higher when compared with the Ravitch procedure. There was also no clear difference noted in patient satisfaction from any of the studies that were part of the meta-analysis.[87] As reported in these studies, advantages of the Nuss repair include shorter operative time, smaller incisions, and less dissection at the potential expense of longer hospital stay, a high complication rate, more difficulty with success in older children and patients with connective tissue disorders, and a paucity of long-term outcome data.[87,88]

## ACQUIRED JEUNE'S SYNDROME

A dreaded complication of surgical correction for pectus excavatum is acquired thoracic chondrodystrophy, or acquired Jeune's syndrome (the congenital syndrome is described later in this chapter) (CXR, Fig. 19-7). This has been described in children referred for severe cardiopulmonary symptoms due to arrested chest wall growth following pectus operations.[51] These children underwent a modified Ravitch surgical repair at a very early age (<4 years old) that involved extensive resections of five or more costal cartilages.

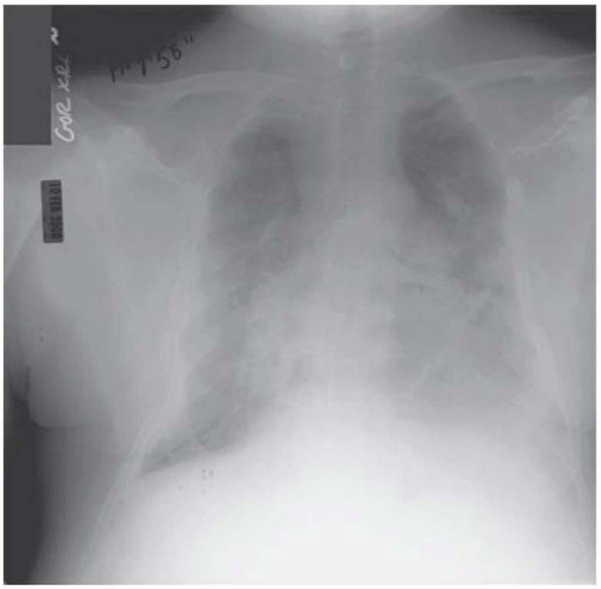


**FIGURE 19-7** Chest x-ray of a patient with acquired Jeune's syndrome. Note the small chest cavity in relation to chest wall and depressed diaphragm.

The restriction of chest wall growth resulted in FVCs of 30 to 50 percent predicted and forced expiratory volumes ($FEV_1$) of 30 to 60 percent.

Acquired Jeune's syndrome should not be mistaken for a recurrence of the pectus excavatum defect. The entire anterior chest wall is hypoplastic, as compared to the reversible depression of the sternum in the case of recurrent pectus. Acquired thoracic chondrodystrophy represents severe restriction of chest wall growth and movement; its natural history includes irreversible pulmonary hypertension.

Diagnosis is best made by clinical examination and CT scanning (Fig. 19-8A and B). Pulmonary function testing reveals very severe restrictive disease, with FEVs and FVCs <30 percent of predicted in most cases. Treatment is extensive and involves excision of all substernal cartilages, mobilization of all of the ribs to the anterior axillary line, and bar stabilization of the sternum. Rib grafts and sternal support bars may be required to stabilize the sternum after such a procedure. The use of rib grafts/compression/expansion plates and substernal support represents attempts to expand the compromised chest cavity. The best treatment for this life-threatening complication, however, is avoidance by delaying Ravitch operative repair in small children until at least the ages of 6 to 8 and minimizing chest wall resection and dissection in younger children.[51]

## RECURRENT PECTUS EXCAVATUM

Up to 5 percent of patients undergoing pectus excavatum repair will have a recurrence following initial surgical correction. The incidence of this is higher in younger patients

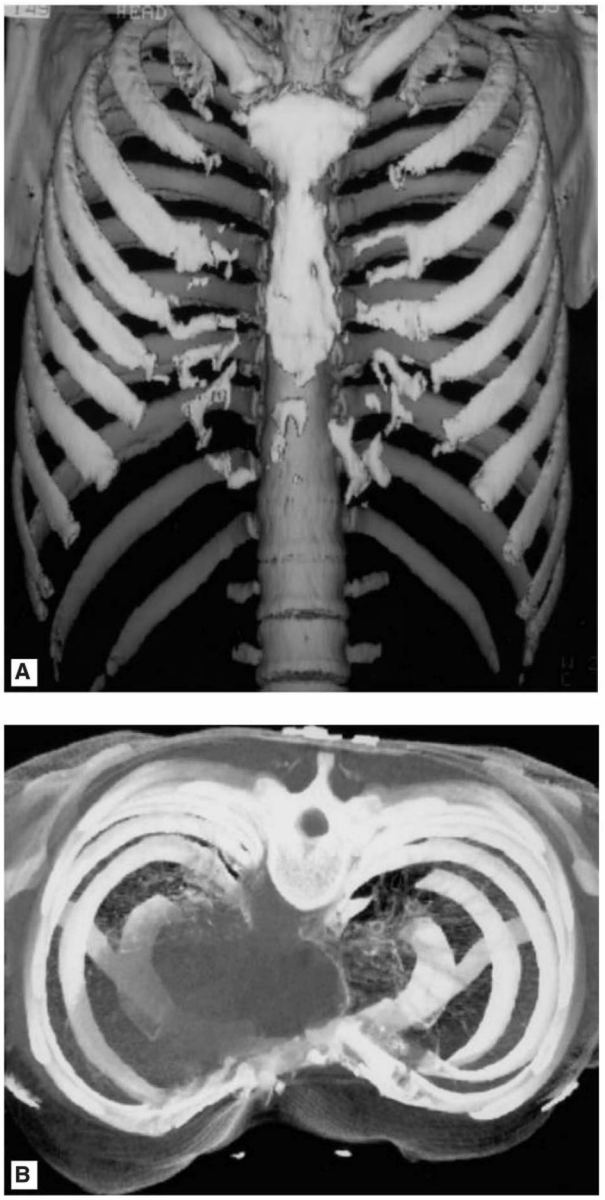



FIGURE 19-8 Recurrent pectus; three-dimensional scan reconstruction with two views (**A** and **B**) of patient with recurrent pectus excavatum.

undergoing repair prior to completion of the teenage growth spurt, in patients with connective tissue disorders such as Marfan's syndrome, and in patients undergoing redo repair.[53,54] Operative repairs using modifications of the techniques of Ravitch or Nuss have been successful.[53,66,83,89]

After a Ravitch repair or one of its modifications, the incidence of recurrence in large studies with long-term follow-up is reported at 2 to 11 percent.[53,63,77,90] One possible cause of recurrence is fibrous nonunion of the edge of the sternum to the costal margin after cartilage resection. As the child progresses through the growth spurt of the teen years, both a fibrous nonunion allowing bending of the sternum and the weight of the chest may play a pathophysiologic role in recurrences, as most are seen in patients below the age of 12 years.[61] If the rib cartilages entirely fail to reattach to the edge of the sternum, an unstable anterior chest wall is created rather than a recurrence, with an easily movable or "floating" sternum.[91]

On initial evaluation of a child with chest wall abnormalities following pectus excavatum repair, a recurrence must be distinguished from a carinatum deformity, an acquired Jeune's syndrome, or a floating sternum. These three deformities are addressed in other sections of this chapter. The severity of the recurrence should be assessed by clinical examination as well as CT scan if necessary. Pretorius and Haller studied the role of spiral CT in evaluating candidates for reoperation and found that CT could accurately define the orientation of the ribs, costal cartilages, and sternum as well as their interrelationships in both the pre- and the postoperative periods. CT findings can help plan an individualized operative repair.[45,92] Pulmonary function tests as well as cardiac output measurements or echocardiography should be performed to evaluate the extent of cardiopulmonary restriction.[28,29]

Indications for reoperative correction are the same as for primary repair and include significant pain, exercise intolerance, a Haller index greater than 3.0, sternal depression greater than 2.5 cm, or significant restriction demonstrated by pulmonary function tests or cardiac evaluation. Timing is critical, and reoperation in teenagers should be postponed until growth spurts have been completed.

The choice of operation depends on the initial operation used to correct the pectus deformity, the type of recurrence, the severity of the defect, the age of the patient, and the experience of the surgical team planning the operation. Successful repairs of pectus recurrences have recently been reported in large series using both modified Ravitch procedures[66,89] and modified Nuss repairs.[83]

Important considerations in preventing recurrence after reoperative Ravitch repairs include the use of a bar placed substernally to elevate the sternum to a neutral position, wiring of the costal cartilages to the edge of the sternum, or repeat subperichondrial resections of the costal cartilages. Wedge osteotomy is usually required, as with primary Ravitch repairs.[6,53,77]

Worldwide experience with Nuss repairs has led to considering the following modifications to primary Nuss repairs as well as reoperations using the Nuss technique. The Lorenz bar is fixated at the point where the bar exits the pleural cavity to first cross over a lateral rib. If the bar is not stable, a second wire is used at the point where the bar crosses a rib in the midaxillary line. Bilateral stabilizing clips are used much more liberally. A second bar is used above the first if the upper sternum remains depressed or below the first if the lower costal margin remains significantly depressed. Finally, in patients with recurrences or connective tissue disorders, placement of the Lorenz bar for periods in excess of the original 2-year recommendation seems

to have decreased problems in these patient populations. VATS is more valuable in reoperative patients as most of these patients do have some pleural adhesions because of their prior operation. An additional port may be necessary to lyse these adhesions. It is important to place chest tubes to help with postoperative hemopneumothoraces, which are more common in this reoperative group. About two-thirds of such patients have an excellent repair with the Nuss procedure. There is a very small (<2 percent) failure rate after the reoperative Nuss procedure.

## PECTUS CARINATUM

### Introduction

The pectus carinatum defect or keel chest mirrors the excavatum defect, with anterior protrusion deformity of the chest wall. Figure 19-9 depicts atypical patient with pectus carinatum. Incidence is about one-tenth that of pectus excavatum, with 0.06 percent of live births with a male predominance pattern like excavatum and a 25 to 30 percent reported family history.[93] Recent work has shown that milder forms of pectus carinatum do exist based on incidental findings on computer tomography.[94] Rotation and lengthening of the costal cartilages causes anterior displacement of the cartilages and resulting sternal protrusion. Carinatum can occur at any age, as early as in the toddler years, but like pectus excavatum, it becomes clinically apparent in the early teenage years. A number of unusual deformities can occur, including unilateral asymmetrical patterns, mixed carinatum/excavatum lesions, and upper chondromanubrial deformities.[94] A number of large clinical reports demonstrate successful surgical correction of carinatum deformities in both male and female patients.[41,47,70,71,93,95–99]

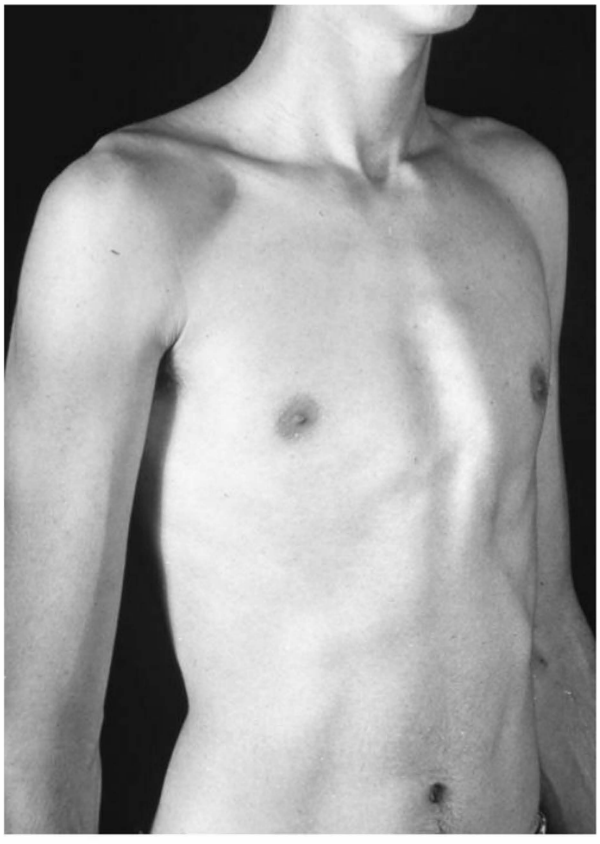


**FIGURE 19-9** Typical pectus carinatum patient with unilateral defect.

### Development and Pathophysiology

As with pectus excavatum, the etiology of pectus carinatum remains unknown. Familial proclivity has been reported,[93] and dominant mutations in the type II collagen gene *COL2A1* have been associated with pectus carinatum.[100] Scoliosis and other spinal deformities or a family history of these are associated with pectus carinatum as well.

Defective and elongated cartilage is responsible for pectus carinatum as well as excavatum. Rapid growth of the cartilages pushes the sternum forward, thus causing carinatum. If these cartilages displace the sternum posteriorly, excavatum occurs.

Since no significant cardiopulmonary abnormalities can be demonstrated with this lesion of the chest wall, carinatum remains a clinical diagnosis and no further diagnostic tests are required. Children with this anomaly do, however, complain on occasion of exertional dyspnea, limitations to exercise potential, frequent respiratory infections, and chest discomfort.[95,96] If necessary, CT scanning can clarify any question of differential diagnosis, better assess the anatomic defect, and help to plan the surgical correction.

Pectus carinatum can cause significant body disfigurement and pain and can have a profound effect on a growing teenager's body image (Fig. 19-10). Indications for surgical correction of pectus carinatum include pain, respiratory symptoms, ease of injury, and psychosocial concerns of body image. Because of a 20 to 30 percent chance of recurrence if this condition is corrected prior to the completion of pubertal growth spurts, repair must be deferred until the patient is fully grown, where the risk of recurrence is less than 1 percent. Table 19-7 outlines typical signs and symptoms of pectus carinatum.

### Operative Repair

Surgical correction for pectus carinatum utilizes the basic principles outlined earlier in this chapter for the modified open Ravitch repair (Table 19-8). Surgical goals include excision of all abnormal cartilages and return of the sternum to a neutral straight position. The same incision and flaps are created as described for patients with pectus excavatum. A meticulous search should be made for abnormal

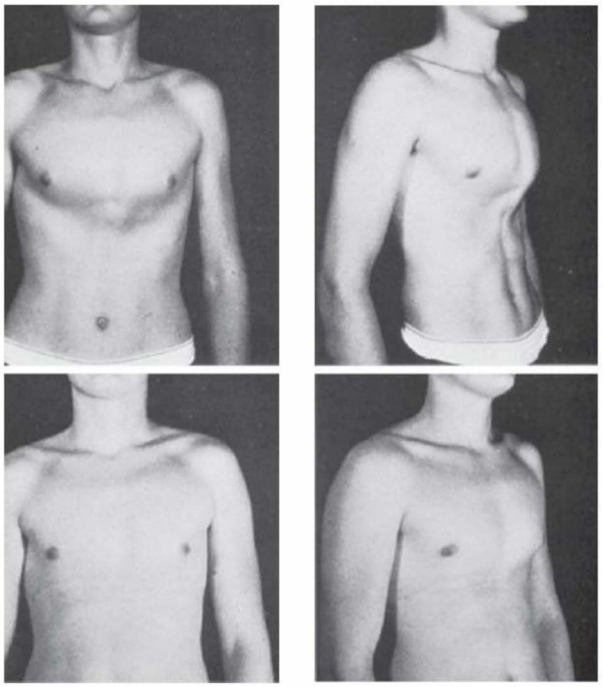


**FIGURE 19-10** Severe pectus carinatum with bilateral involvement of costal cartilages and elevation of the sternum; pre- and postoperative views.

cartilages, since they may be difficult to identify and those that go unrecognized are sources of recurrence. All abnormal cartilages, usually bilaterally, are resected using the subperichondrial technique of Ravitch. If the sternum remains anterior or rotated after subperichondrial resection, anterior sternal osteotomies can be performed to facilitate depression of the anterior table of the sternum to a neutral position. Oblique osteotomy corrects sternal rotation. In our institution, we use subpectoral and subcutaneous drains to avoid seromas. Hospital stay is usually 3 to 4 days, and neocartilage formation of 6 to 8 weeks' duration precludes contact sports or strenuous activity for this postoperative period.

**TABLE 19-7: Signs and Symptoms of Pectus Carinatum**

| |
|---|
| Physical signs |
| Sternal elevation/rotation |
| Unilateral or bilateral costal cartilage elevation |
| Barrel chest |
| Symptoms |
| Parasternal pain |
| Frequent injuries |
| Exercise intolerance |
| Decreased work capacity |

**TABLE 19-8: Key Components of Pectus Carinatum Repair**

1. Transverse or midline incision
2. Skin subcutaneous and muscle flaps
3. Excision of all elevated cartilages
4. Contralateral cartilage resection (if unilateral)
5. Anterior sternal osteotomy to depress sternum to neutral position
6. Bone wedge to hold sternum in neutral position
7. Wound closure with closed drainage

## Outcomes and Complications

Fonkalsrud and Beanes have described their 30-year experience with 90 children who underwent surgical repair of pectus carinatum defects.[96] All of the children were symptomatic, including 84 with exertional dyspnea and exercise limitation, 52 with respiratory infections, 24 with asthma, and 38 with pain. Modified Ravitch-type repairs were used in all patients. Deaths were none and complications were minimal, with only 5 patients developing seroma, 3 with pleural effusions, and 2 with pneumothorax. Mean hospital stay was 2.6 days and follow-up was 12.8 years. The authors described one recurrence amenable to reoperation, and all children reported marked clinical improvement. Similar success, although with greater technical difficulty, has been reported with pectus carinatum repair in adults.[41,47,71]

Two other large series have reported success in the surgical correction of pectus carinatum defects. Saxena and Willital reviewed a 14-year experience of 111 patients using double bilateral chondrotomy and retrosternal mobilization and stabilization with metal struts; they reported 98 percent success, 1.8 percent major recurrences, and 2.7 percent minor recurrences.[99] Shamberger and Welch reported a 12-year experience of 152 pectus carinatum repairs utilizing bilateral resection of costal cartilages and osteotomy, with satisfactory results in all patients and only a 3.9 percent complication rate, including pneumothorax, wound infection, atelectasis, and local tissue necrosis. Experience at our own institution has been similar, with virtually no recurrence in patients corrected after maximal growth.[98]

# OTHER CHEST WALL ANOMALIES

## Poland's Syndrome

Alfred Poland, as a medical student affiliated with Guy's hospital, is credited with having described, in 1841, the congenital absence of pectoralis major and minor muscles, although this had previously been reported in the French and German literature in 1826 and 1839, respectively.[101–103] Poland's finding was attributed to his name in 1962 by Clarkson of the same hospital.[104] Poland's syndrome or

pectoral aplasia is a spectrum of deficiency or absence of components of the chest wall, including the pectoralis major, pectoralis minor, serratus anterior, ribs 2 to 5, and the breast and areolar complex.[105] Associated hand deformities include brachydactyly, syndactyly, and ectromelia.

The incidence of this disease is approximately 1 in 30,000 live births.[106,107] Shamberger and associates recently reported a 33-year 75-patient experience with Poland's syndrome.[108] Of these patients, 40 were male and 35 female; 44 were right-sided, 30 left-sided, and 1 bilateral. Absence of the pectoralis major and minor muscles or their significant hypoplasia was described in all patients. The spectrum of chest wall involvement included 41 patients with normal chest walls, 10 with hypoplasia of the ribs, 11 with major depression deformities and 5 with minor depression deformities of the ribs, and 8 with complete aplasia of the ribs.

In its most severe form, the classic presentation of Poland's syndrome involves herniation of the lung through the chest wall defect during coughing or crying in a newborn. For this flail segment, prompt repair is necessary. Without lung herniation, toddlers with this syndrome can be observed until adolescence, when the remaining muscles of the chest wall have reached a size sufficient to facilitate repair. Repair should be timed based on clinical symptoms, cosmetic abnormalities, and the age and physical build of child.

Successful surgical repair using autologous rib grafts,[108] latissimus muscle flaps,[109] synthetic mesh,[110] or a combination of these modalities has been described. CT is an acceptable means of evaluating these patients after surgical repair. Figure 19-11 shows a typical patient before and after repair. Postoperative recurrence is unlikely and can be repaired with rewiring of the original bone or cartilage grafts to the sternum and native rib cage or with autologous grafts and mesh similar to the procedure in primary repair.

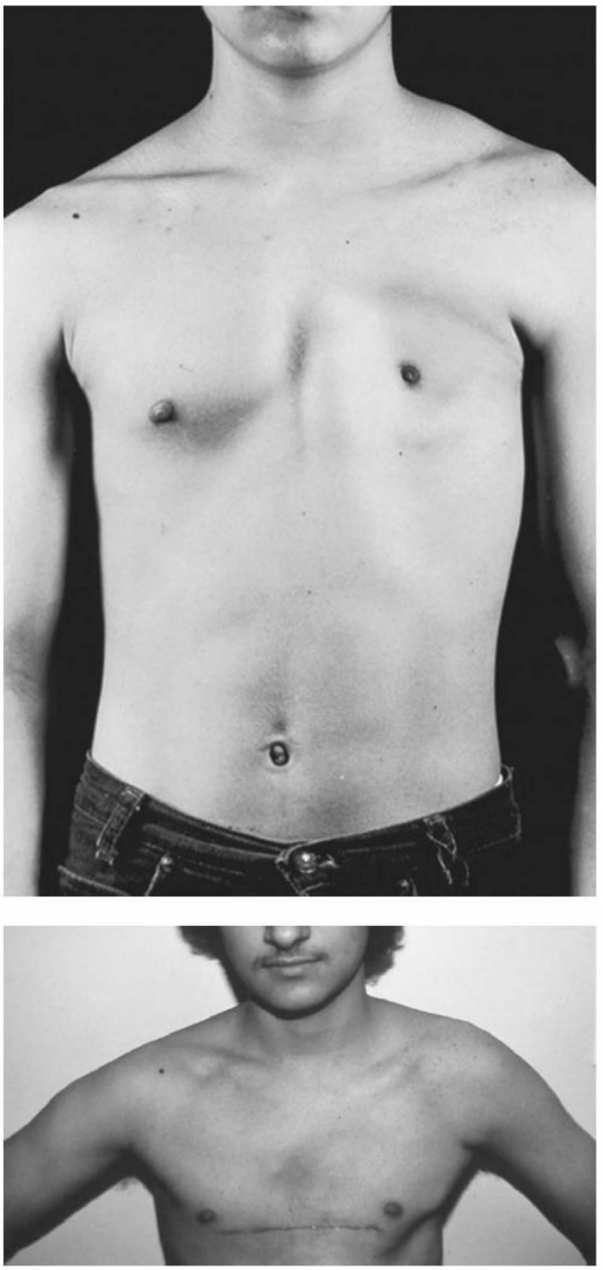


**FIGURE 19-11** Teenager with right-sided Poland's syndrome; pre- and postoperative views.

## Pentalogy of Cantrell

A syndrome of lower sternal cleft, epigastric or high omphalocele, anterior diaphragmatic defect, absent pericardium, and an intracardiac anomaly was originally described in 1958 by Cantrell.[10] The developmental etiology is unknown, but it has been suggested to relate to anomalies in defined subunits of a ventral midline developmental field.[111] As with all developmental syndromes, a spectrum of clinical manifestations can be found. The heart is usually found within the omphalocele defect and, if the omphalocele ruptures, an ectopia cordis can be created (Fig. 19-12). Regardless, immediate surgical attention is warranted in any case of pentalogy of Cantrell. Staged repair is usually required to first close the epigastric omphalocele, repair the diaphragmatic defect, and effect skin coverage of the heart. Secondary procedures to obtain bony coverage of the heart may be delayed for 2 to 3 years to allow for adequate growth. Repair of the intracardiac defect is usually deferred until after somatic closure, although in rare instances simultaneous repair can be accomplished.

## Jeune's Syndrome

Originally described by Jeune in 1954,[9] the syndrome of asphyxiating thoracic chondrodystrophy ranges from a lethal condition at birth to a survivable and surgically treatable disorder.[112] The original patient described had a narrow, rigid chest wall and multiple cartilaginous anomalies and died early in the perinatal period from respiratory insufficiency.

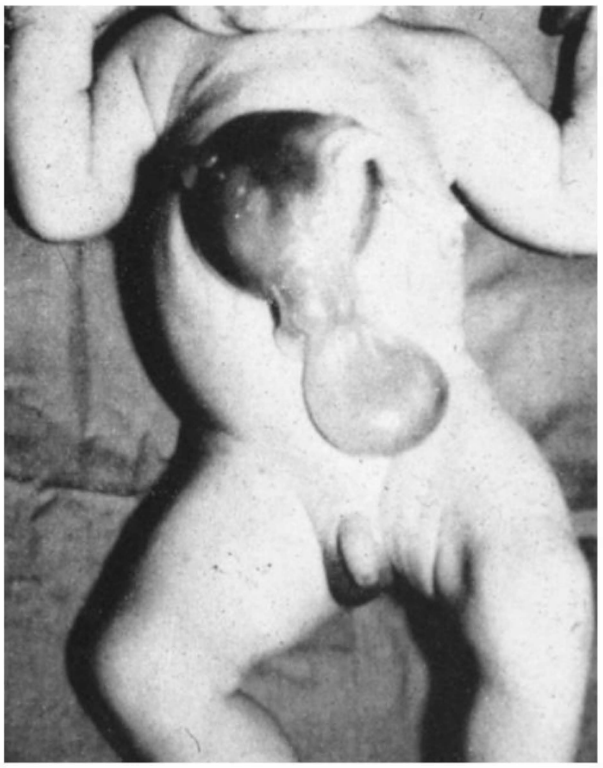


**FIGURE 19-12** Photograph of a newborn infant with pentalogy of Cantrell. Note the upper omphalocele, foreshortened sternum with defect, and pericardial defect.

An autosomal recessive pattern of inheritance has been described, but not in association with known chromosomal abnormalities.[113]

Clinical features include a narrow thorax along both the transverse and the sagittal axes, protuberant abdomen, little respiratory movement of the chest wall, short and wide ribs, costochondral junctions that are splayed and barely reach the anterior axillary line, and irregular costal cartilage. Associated findings include short extremities with relatively wide bones, fixed and elevated clavicles, and a small hypoplastic pelvis (Fig. 19-13A and B). Pulmonary development can also be abnormal; findings vary from patient to patient.[114]

Operative repair offers limited success and is usually performed when children are on oxygen and may be ventilator-dependent. Available modalities for surgical chest wall expansion include sternal splitting, anterior chest wall release, autologous grafts, artificial ribs, stainless steel support struts, and mesh and other prostheses. After axial growth, further procedures may be required to facilitate chest wall expansion. The limiting factor for survival following surgical correction is not the chest wall itself but the underlying pulmonary hypoplasia.

## Cleft Sternum

Failure of ventral fusion of the thoracic wall causing cleft sternum or sternum bifidum is extremely rare, and the largest series in the literature comprise fewer than 10 patients

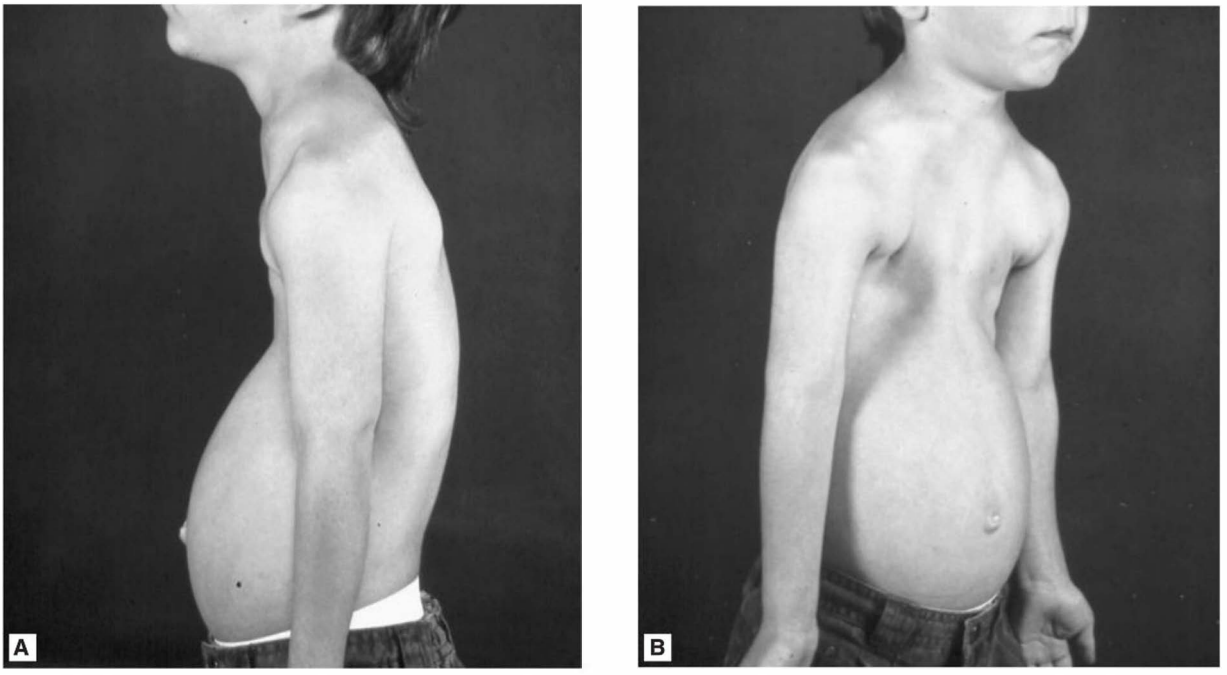



**FIGURE 19-13** Patient with congenital Jeune's syndrome. The lateral view (**A**) shows a marked decrease in the AP diameter of the chest, while the anterolateral view (**B**) shows marked undergrowth of ribs.

each.[115–117] Associated malformations include congenital cardiac abnormalities, maxillofacial hemangiomata, and omphalocele.[115,118] The goals of surgical correction of the split sternum are bony protection of the heart, great vessels, and other mediastinal structures as well as anterior thoracic stability to maintain normal physiologic pressures for the support of respiratory function and circulation.[118,119]

Cleft sternum can be classified into superior, inferior, and total. This is based on where the cleft exists on the sternum proper. Patients will notice paradoxical deepening of the sternum on inspiration and protrusion with coughing or expiration. Occasionally, the heart can be seen pulsating under the skin.

Repair of sternal clefts is best performed in the neonatal period, where primary repair is possible.[115,117,118,120,121] Isolated reports have demonstrated some success of surgical correction in adults as well, using bone grafts, muscle flaps, sliding chondrotomies, posterior sternal wall repairs, posterior periosteal flaps, sternal bars, and chondral grafts.[117, 118,121–124]

Acastello and coworkers recently reviewed their experience with 8 patients over a 14-year period, 6 (75 percent) of whom were female, who underwent surgical correction of sternal cleft with 1- to 8-year follow-up.[115] Three methods were used: (1) primary closure; (2) partial resection of the upper three costal cartilages and disruption of the sternoclavicular junction, followed by closure of the sternal bars with wire; and (3) mobilization and approximation of sternocleidomastoid muscles with costal homograft and mesh. All three groups fared relatively well, although one patient in group 3 had an unsatisfactory result and required reoperation with the technique of group 2. The patients corrected with primary repair had the best outcomes, although mild pectus excavatum developed in some in the long term.

## Minor Anomalies

A number of chest wall anomalies may occur that usually require specific diagnosis but may not require operative intervention. Rib anomalies include fusion, partial absence, and growth deformities. Similar findings may occur with the costal cartilages, particularly in the costal margin area of the lower chest. Most of these anomalies do not require surgical intervention unless there is instability of the chest wall or significant body image issues exist. Most anomalies for which operative repair is contemplated should be observed until children reach school age or complete teenage growth.

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## CONGENITAL CHEST WALL ANOMALIES BOARD REVIEW QUESTIONS (CHAPTER 19)

1. Which of the following statements is incorrect regarding repair of pectus excavatum in children?
   A. Repair should be avoided during pubertal growth spurt.
   B. Repair has good outcomes before pubertal growth spurt.
   C. Repair has good outcomes after pubertal growth spurt.
   D. Puberty has predictable effects on chest wall morphology.

2. Which of the following is correct regarding pectus excavatum?
   A. Pectus excavatum is associated with trisomy 18.
   B. Pectus excavatum does not occur in patients with Ehlers–Danlos syndrome.
   C. Up to two-thirds of children with Marfan's syndrome have pectus excavatum.
   D. Patients with connective tissue disorders do not achieve the similar functional results after repair of pectus excavatum compared with the average patient.

3. Patients with Jeune's syndrome:
   A. May have an autosomal recessive pattern of inheritance
   B. Typically have chromosomal abnormalities
   C. Have normal pulmonary development
   D. Have best results from surgery when asymptomatic

4. Which is correct regarding repair of pectus excavatum with the Nuss procedure?
   A. Bilateral chest tubes should be placed at the end of the operation
   B. Retrosternal dissection should be carried out from right to left side
   C. Dissection may be performed using thoracoscopy
   D. The Nuss procedure should be reserved for children and adolescents

5. Which is true regarding the preoperative workup for repair of pectus excavatum?
   A. Psychological factors have little impact in children.
   B. Repair is indicated for a Haller index of 3 or above.
   C. Patients do not need pulmonary function studies unless they require oxygen at home.
   D. Preoperative dyspnea on exertion related to pectus excavatum is unlikely to be improved.

## ANSWERS

1. **Answer: D.** Proper timing of surgical repair is essential for adequate outcome, although this is also frequently debated and based on retrospective data. In general, good results have been reported with correction in school-aged children between the ages of 8 and 16, either before or after but not during their pubertal growth spurts. Repair during growth spurts is not recommended because of the variable change in the morphology of the child's chest during this time.[15,42,49] There is a slight advantage of undergoing a repair before puberty, which is the ability of the bar to stabilize the malleable chest during this period and throughout the puberty spurt.
2. **Answer: C.** Pectus excavatum is relatively common, occurring in approximately 1:400 live births, with a male predominance of up to 5:1.[15] No genetic abnormalities or chromosomal aberrations have been associated with pectus excavatum, although a familial tendency has been described.[15,16] Up to two-thirds of children with Marfan's syndrome and a high frequency of Ehlers–Danlos patients develop pectus excavatum deformities.[3,4] Children with connective tissue disorders can present later in life, have more progressive defects, and suffer from more complicated postoperative courses, but successful cosmetic and functional results can be achieved even in these patients.[4]
3. **Answer: A.** An autosomal recessive pattern of inheritance has been described in patients with Jeune's syndrome, but not in association with known chromosomal abnormalities.[113] Pulmonary development is typically abnormal; findings vary from patient to patient.[114] Operative repair offers limited success and is usually performed when children are on oxygen and may be ventilator-dependent. Available modalities for surgical chest wall expansion include sternal splitting, anterior chest wall release, autologous grafts, artificial ribs, stainless steel support struts, and mesh and other prostheses. After axial growth, further procedures may be required to facilitate chest wall expansion. The limiting factor for survival following surgical correction is not the chest wall itself but the underlying pulmonary hypoplasia.
4. **Answer: C.** During the Nuss procedure, a retrosternal tunnel is created to allow passage of the bar in the retrosternal space. A Crawford clamp or similar device is carefully advanced by blunt dissection from the left hemithorax to the right side. For this maneuver, bone hook elevation of the distal sternum or video-assisted thoracoscopic surgery (VATS) may be helpful. We insist that the clamp pass from left to right to minimize potential injury to the heart and great vessels. Pneumothoraces on both sides are evacuated at the end of the operation with a sustained Valsalva maneuver; routine chest tube placement is not necessary. The Nuss procedure can be performed on older adolescents and adults; there is no specific age contraindication in the adult population.
5. **Answer: B.** Factors determining candidates for repair of pectus excavatum defects include anatomic, physiologic, psychological, considerations as well as proper timing (Table 19-2). A CT scan can accurately define the anatomic defect, including the severity index of the sternal depression as well as its effects on cardiac and pulmonary anatomy. A Haller index of 3 or greater is an indication for surgery.

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# 20 Benign Pleural Disorders

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## KEY CONCEPTS

The pleura are anatomically and physiologically distinct structures. The pleural cavities are formed early during embryonic development from the intraembryonic coelom. Anatomically, the pleura are divided into two structures: the visceral and the parietal pleura. The visceral pleura lines the lungs and is intimately invested with the lung parenchyma. The parietal pleura lines the chest wall, diaphragm, mediastinum, and the superior portion of the lungs.

- Pathophysiology
  - The pleura and pleural fluid production are tightly regulated anatomical and physiologic entities. The pleura function as serous membranes that line the lungs and chest wall by creating a sealed space between the lungs and atmosphere, allowing for the development of distinct intrathoracic pressures necessary for respiration and the production of pleural fluid. Pleural fluid serves as a lubricant as well as a mechanical coupler between the chest wall and the lungs during respiration. The pleural cavity is a potential space that exists until various pathologic processes interrupt the normal anatomy or physiology of the space, exposing the cavity. Air, excess pleural fluid, chyle, infections, and fibrous tissue are all potential pathologic entities that can disrupt the pleura and pleural space.
- Clinical features
  - Patients presenting with pleural disorders often complain of a myriad of symptoms; however, most commonly patients will present with one or more of the following: dyspnea, chest pain, and cough. The history and physical examination help to differentiate the etiology of these symptoms. Questions that investigate the onset and duration of these symptoms, their character, and past medical and surgical history can all be illuminating. The physical examination is indispensable in investigating pleural diseases. Dullness or hyperresonance on percussion, decreased or increased tactile fremitus, breath sounds, and visual inspection of the chest wall and respiratory pattern can further refine the diagnosis.
- Diagnostics
  - Diagnosing pleural disorders often starts with a standard posteroanterior and lateral chest x-ray. The lungs, chest wall, and mediastinum are visualized, and if a pathologic process occurs, the pleural cavity is also visualized. More advanced visualization techniques such as a computed tomography (CT) scan and ultrasound may be necessary to further define the process. In some cases, invasive techniques (i.e., thoracentesis in pleural effusions) are required to finalize a diagnosis.
- Management
  - Benign pleural disorders are a diverse group of diseases that require complex management and often a combination of both medical and surgical approaches. For example, for pneumothoraces, conservative management involves evacuating the pleural space. If conservative management fails or there is worsening of the disease or recurrence, the patient proceeds to surgical therapy. Conservative management attempts to decrease the disruption within the pleural space and treat the underlying cause. Surgery is often reserved for refractory cases or patients with contraindications to conservative management.
- Outcomes and prognosis
  - The term "benign" is misleading in describing nonmalignant pleural disorders. If left untreated or not properly treated, these diseases can lead to significant morbidity and even mortality. Some disease processes do recur and ultimately require more extensive surgical management or chronic conservative treatment. However, with prompt and appropriate treatment, patients can be managed effectively, and morbidity and mortality rates reduced significantly.

# INTRODUCTION

The pleura and lung work in concert to perform the mechanics of respiratory function. The potential space between the pleura and lung provides negative pressure, serves as a lubricant, and is a mechanical coupler between the lung and chest wall during respiration. This delicate balance can be interrupted by benign processes that alter the normal anatomy of the pleura and pleural space. With an estimated incidence of 1.5 million pleural effusions in the United States annually, an understanding of the diagnosis and treatment of this and other benign pleural diseases is valuable in one's clinical armatorium.

# PLEURAL EMBRYOLOGY

## Formation of the Pleural Cavities

The pleural cavities are formed during the fourth week of embryonic development. Initially, the septum transversum evaginates into the intraembryonic coelom separating the coelom into a primitive pericardial cavity and peritoneal cavity. The septum transversum migrates to its final position inferior to the lung buds, where it eventually forms part of the diaphragm. The primitive pericardial cavity is separated into the pleural and pericardial cavities by pleuroperitoneal folds that grow from the lateral walls of the cavity medially. The medial fusion of these projections forms three distinct cavities: the two lateral pleural cavities and the medial pericardial cavity. Inferiorly, the pleural cavities communicate with the peritoneal cavity but are eventually closed by dorsoventral growth from the pleuroperitoneal membranes (failure to close in the fetus results in congenital diaphragmatic hernia).[1,2]

## The Pleura

The lung forms from a respiratory bud that evaginates from the embryonic foregut and grows ventrally into the newly forming pleural cavities. The respiratory epithelium of the lungs is derived from the endodermal cells of the foregut; however, the supportive cartilage, muscle, and the visceral pleura are formed from the mesoderm that the respiratory bud is surrounded by as it evaginates. The mesoderm, which composes both the visceral and the parietal pleura, differentiates into a single layer of mesothelial cells and a supportive tissue forming a serous membrane that allows frictionless movement in the pleural cavity as the lungs expand and retract.[1,2]

# PLEURAL ANATOMY

## Gross Anatomy

In adults, the pleura is divided into the visceral and parietal pleura. The visceral pleura is a thin serous layer that completely invests the lungs, including the fissures. There is no separation between the visceral pleura and the lung parenchyma. The blood supply to the visceral pleura is through the bronchial arteries, and venous drainage through the pulmonary veins. Lymphatic drainage of the visceral pleura occurs primarily through deep pulmonary plexuses within the lung parenchyma at the interlobar and peribronchial spaces. The visceral pleura is not innervated by the somatic nervous system.

The parietal pleura lines the chest wall, diaphragm, portions of the pericardium and mediastinum. Thus, the parietal pleura has distinct anatomical names; the costal pleura, diaphragmatic pleura, pericardial pleura, mediastinal pleura, the cupula of the pleura, or cervical pleura, where the pleura reflects over the superior portion of the lungs. The cupula protrudes into the anterior inferior neck, posterior to the sternocleidomastoid muscle, extending approximately 2 to 3 cm cephalad from the superior border of the first rib. The parietal pleura tightly adheres to both the diaphragm and the pericardium, but is dissectible from the ribs, cupula, and mediastinum. Arterial blood is supplied to the parietal pleura through branches of arteries supplying the ribs, diaphragm, and mediastinum. Venous drainage is through the veins running parallel with the arterial supply, and direct drainage into the superior vena cava. Lymphatic drainage of the parietal pleura occurs anteriorly through the internal mammary nodes, posteriorly into the intercostal nodes, and the diaphragmatic parietal pleura drains into the retrosternal and mediastinal nodes. The parietal pleura is innervated by the somatic, sympathetic, and parasympathetic nervous system through the intercostal nerves. Similarly, the diaphragmatic parietal pleura is innervated through the phrenic nerve.

The visceral and parietal pleura are continuous with each other at the lung hilum. At the inferior lung root, the reflections of anterior and posterior pleura come together along the mediastinum and extend inferiorly to the diaphragm, forming the pulmonary ligament. The pulmonary ligament functions to anchor the inferior lung to the diaphragm.

In healthy adults, only a thin layer of serous fluid separates the parietal and visceral pleura. Normally, the pleural cavity is a potential space that exists between the visceral and parietal pleura. This cavity becomes apparent when large amount of fluid or air is present during pathologic processes. The lung fills the pleural cavity almost entirely, except for the inferior recesses of the diaphragm and the anteriomedial mediastinum posterior to the sternum. These spaces are known as the phrenicocostal sinus and costomediastinal sinus. These sinuses are the earliest sites of excess fluid accumulation during pathologic processes.

## Histology

The pleura consist of five layers: (1) an innermost mesothelial cell layer, (2) a submesothelial interstitial connective tissue layer, (3) an inner thin elastic fiber layer, (4) an outer interstitial connective tissue layer, and (5) a thick elastic fiber layer. The mesothelial cells are lined with microvilli.[3]

The microvilli function to increase surface area of the mesothelium thereby serving two functions: (1) cellular transport and metabolic activities related to pleural fluid reabsorption and (2) enmesh glycoproteins that aid in lubricating the pleura, decreasing friction during lung movement.[4] These functions are supported by the geographic distribution of the mesothelium with microvilli. In general, the visceral pleura contains more cells with microvilli than the parietal pleura, and the density of microvilli increases caudally. This is due to the role the visceral pleura plays in reabsorption of the pleural fluid, and the increased friction at the base of the lung, respectively.

## PHYSIOLOGY OF THE PLEURA

### The Pleura

The pleura serves three primary functions. First, the pleura forms a serous layer over the lung and chest wall, preventing adhesions of the lung to the chest wall and allowing for easy deformation of the lungs when in contact with other structures (i.e., the pericardium or diaphragm). Second, the pleura produces pleural fluid, whose function will be described later. Finally, the pleura acts as a barrier between the atmosphere and the alveolar space allowing for the development of distinct intrathoracic pressures necessary for normal respiration.[4–6]

### Pleural Fluid

Pleural fluid is produced primarily by the parietal pleura through the capillaries feeding the parietal pleura. The negative intrathoracic pressure produces a hydrostatic pressure that counteracts the oncotic pressure within the capillaries, thus favoring fluid movement into the pleural cavity. Pleural fluid is absorbed by the visceral pleura through passive and active uptake by the mesothelial cells as well as lymphatic stomas within the parietal pleura. Roughly 3.4 mL/kg of fluid is produced per day by the pleura; however, only 0.1 to 0.3 mL/kg of fluid is present in the pleural cavity at any given time.[5,6]

The fluid serves two important functions. The first is converting the shearing perpendicular forces generated by the chest wall and diaphragm that are exerted onto the lung into sliding forces, thereby, coupling the movement of chest wall and lung expansion.[5] Second, it provides lubrication for the lung and chest wall, which decreases friction of movement during respiration, thus decreasing the amount of work required for respiration.

## PNEUMOTHORAX

### Definition

A pneumothorax is defined as air in the pleural cavity. Air enters the pleural space by two primary methods[7]:

**TABLE 20-1: Causes of Pneumothorax**

| |
|---|
| Spontaneous |
| Primary spontaneous |
| No underlying respiratory disease, often ruptured bullae or blebs |
| Secondary spontaneous |
| Underlying respiratory disease, most commonly COPD |
| Traumatic |
| Noniatrogenic |
| Blunt or penetrating thoracic trauma |
| Iatrogenic |
| Invasive thoracic procedures |
| Tension |
| Catamenial |

1. Communication between the pleural cavity and the atmosphere.
2. Communication between alveolar air and the pleural cavity.

Clinically, pneumothoraces can be divided into four major categories: spontaneous, traumatic, tension, or catamenial. Table 20-1 lists the causes of pneumothorax.

### Clinical Features

Symptoms of a pneumothorax can be diverse and are often dependent on concomitant disease and methods of presentation. For spontaneous pneumothoraces, sudden onset of dyspnea, unilateral pleuritc chest pain, and cough are the most common symptoms. The chest pain often resolves within 24 h and the dyspnea is dependent on the size of the pneumothorax, but usually it is a minor symptom in an otherwise healthy patient.

### Diagnosis

The physical examination can be helpful if the pneumothorax is significant. Decreased breath sounds and tactile fremitus in the area of the pneumothorax as well as hyperresonance on percussion can be present. However, it is important to remember that small pneumothoraces will often have normal examinations and clinical suspicion of a pneumothorax should be investigated further.

The radiographic modality of choice is an upright posteroanterior or lateral (with the affected side superior) chest x-ray. Findings on x-ray include a thin pleural line displaced from the chest wall often accompanied by a radiolucent area devoid of lung markings. Small pneumothoraces may be difficult to evaluate on chest x-ray and computed tomography (CT) scans may be necessary. However, CT scans should not be routinely employed to diagnose a pneumothorax.

True tension pneumothorax is a rare, but clinically significant manifestation. It is important to be able to recognize physical signs of a tension pneumothorax, as delay in

diagnosis can be catastrophic. Often these patients present with symptoms mentioned earlier, but the dyspnea is out of proportion to the common presentation and is accompanied by diaphoresis, tachycardia, cyanosis, hypotension, and deviation of the trachea away from the affected side. These symptoms are a result of air trapping within the pleural cavity causing a shift of the mediastinum as well as reduced preload and stimulation of the sympathetic nervous system.[8] Prompt recognition and resolution is vital, and radiology is often deferred until treatment has been instituted.

## Spontaneous Pneumothorax

Spontaneous pneumathoraces can be subdivided into primary spontaneous pneumothorax (PSP) and secondary spontaneous pneumothorax (SSP). A PSP is a pneumothorax that develops without insult in a patient with no underlying pulmonary disease. Classically, these patients are tall, thin, young adult males, who are found to have ruptured apical subpleural pulmonary blebs. The etiology of pulmonary blebs is often unclear, but it has been postulated to be due to heredity, congenital malformations, or distal airway inflammation. PSPs have a reported incidence of 7.4 to 18 cases/100,000 per year in males and 1.2 to 6 cases/100,000 per year in females. Roughly, 20,000 new cases are reported annually in the United States. Patients are usually between the ages of 10 and 30 years, and cigarette smoking is a significant risk factor.[9]

SSP occurs without warning in patients with known pulmonary disease. The most common pulmonary disease associated with SSP is chronic obstructive pulmonary disease. Children with underlying pulmonary disease, such as cystic fibrosis, can also present with SSP. Clinically, these patients often present in severe respiratory distress due to the existing respiratory dysfunction. SSPs have a reported incidence of 6.3 cases/100,000 in males and 2 cases/100,000 in females.[9]

## Traumatic Pneumothorax

There are iatrogenic and noniatrogenic traumatic pneumothoraces. Noniatrogenic pneumothoraces are commonly encountered with patients presenting with either blunt or penetrating thoracic trauma. Pneumothorax is the second most common sign of thoracic trauma, occurring in up to 50 percent patients.[10] In these cases, the diagnosis of pneumothorax may be unclear, but in any patient requiring mechanical ventilation after thoracic trauma, a chest tube should be placed and a CT scan obtained.[8]

Iatrogenic pneumothoraces are the most common nosocomial pneumothorax. Pneumothorax occurs following transthoracic needle biopsy (24 percent), subclavian vein catheterization (22 percent), thoracentesis (20 percent), transbronchial lung biopsy (10 percent), pleural biopsy (8 percent), and positive-pressure ventilation (7 percent).[11] Iatrogenic pneumothorax is often a result of physician's inexperience with the procedure and therefore diagnosis is often delayed.

## Tension Pneumothorax

The etiology of tension pneumothorax is often multifactorial. The underlying pathophysiology is an injury that allows air to enter the pleural space without subsequent removal leading to the development of positive intrathoracic pressures, which cannot be overcome by the respiratory cycle.[12] Thoracic trauma is the most easily recognized cause of tension pneumothorax, but other etiologies exist. Spontaneous pneumothoraces can evolve into tension pneumothorax if the parenchymal lesion is not contained with the initial collapse. Iatrogenic pneumothoraces, such as barotraumas, and puncture injures can lead to tension pneumothoraces as well. Treatment of tension pneumothorax should be done promptly and judiciously. The most common primary treatment is decompression with needle thoracostomy. Needle thoracostomy allows for rapid resolution and does not require the procedural skills necessary for tube thoracostomy. However, the definitive therapy for a tension pneumothorax is tube thoracostomy, and therefore placement of a chest tube should not be delayed. Needle thoracostomy is a temporizing agent.

## Catamenial Pneumothorax

Catamenial pneumothorax is a rare form of spontaneous pneumothorax. It generally occurs in women aged 30 to 40 years. The pneumothorax most often presents between 24 and 72 h after the onset of menstruation. Several theories have been postulated as to the cause, but most commonly, the presence of pelvic or thoracic endometriosis leading to perforation of the diaphragmatic pleura and the introduction of air into the pleural space are the causes. Treatment for catamenial pneumothorax is separate from other types of pneumothoraces, as the first occurrence requires surgical management due to the high probability of recurrence. Mechanical pleurodesis along with closing any openings within the pleura that are visualized should be instituted. Hormonal therapy exists as an option as well; however, the side effects are significant and patients should be counseled on its implementation.[8]

## Management

Management of pneumothoraces is often complex and dependent on multiple variables, such as size of the pneumothorax, hemodynamic stability, associated symptoms, concomitant disease, and primary or recurrent pneumothorax. Management options are observation, aspiration, tube thoracostomy, pleurodesis, and surgery. Observation is generally reserved for small spontaneous pneumothoraces

without significant symptoms. Inhaled supplemental oxygen can be instituted in these patients. These patients should be observed in the hospital, as enlargement of the pneumothorax is possible.

Aspiration can be used in patients with a mild-to-moderate pneumothorax. Aspiration allows for evacuation of the pleural cavity and complete lung expansion. Studies have demonstrated that needle thoracostomy carries a risk of minimal complications and patient discomfort as well as success rates comparable with tube thoracostomy.[7] When performing an aspiration, the needle can be placed in either the second intercostal space in the midclavicular line or the fifth intercostal space in the midaxillary line, similar to tube thoracostomy. The needle is generally attached to either a stopcock, allowing for manual aspiration, or a one-way valve. Follow-up chest x-ray should be obtained to confirm resolution of the pneumothorax. If the pneumothorax does not resolve, tube thoracostomy should be employed.

Larger pneumothoraces or those causing significant symptoms should be treated with a chest tube. The chest tube should be placed in the fifth intercostal space in the midaxillary line. Creating a subcutaneous track can help prevent air leaks and aid in positioning of the chest tube. The tube should be directed posterior and superior. At our institution, we add additional holes to the chest tube to aid in drainage of pleural effusions at the inferior portion of the pleural cavity (it must be kept in mind to place the final hole through the radiopaque line so that proper placement can be visualized on chest x-ray). On initial placement, the chest tube is placed on suction. Once re-expansion has been demonstrated for 24 h, the chest tube can be placed on water seal.

Tube thoracostomy is 90 percent successful in resolving a first occurrence of a PSP, 50 percent for a first recurrence, and 15 percent for second recurrence. PSPs have been reported to recur in 33 percent of patients, 62 percent of those patients will recur a second time, and 83 percent of those a third time.[8,9] Prophylactic treatment to prevent recurrence of PSPs is generally not recommended after the initial pneumothorax, but patients who report recurrence are recommended for treatment.

Pneumothorax recurrence can be treated through two options, chemical pleurodesis or operative management. Chemical pleurodesis is employed in patients who are not good operative candidates or those who refuse surgery. The agents most commonly used are one of the tetracycline antibiotics and sterile talc. The agent is infused through the chest tube and the patient rotated side to side to distribute the chemical. Recurrence rates are high with chemical pleurodesis.

Surgical indications include recurrence as well as bilateral spontaneous pneumothoraces, persistent air leaks, and incomplete lung re-expansion. Patients at high risk of reoccurrence (i.e., aviation personnel, scuba divers) are often treated operatively after a primary occurrence. Operative management consists of irritation of the pleura with or without parenchymal removal. Thorough pleurodesis is the primary goal of the procedure. This is generally accomplished by both mechanical pleurodesis as well as the use of a chemical sclerosant. Visualization of bulla or blebs is a relative indication for removal. Removal without pleurodesis results in high recurrence rates.[7] The most common surgical approach is video-assisted thoracoscopic surgery (VATS) but thoracotomy may be necessary depending on the clinical situation.

## PLEURAL EFFUSIONS

### Definition

A pleural effusion is defined as an excess of pleural fluid within the pleural cavity. This is generally considered to be an accumulation of 500 mL or more in the pleural space. As mentioned previously, the pleural fluid serves an important function in coupling the movement of the chest wall with movement of the lungs. This coupling depends immensely on the volume of pleural fluid present, as an increase in volume will decrease the amount of force that is transmitted from the movement of the chest wall to the lung. Excess fluid accumulates through three possible mechanisms[5]:

1. Change in pleural pressure balance
2. Impaired lymphatic drainage
3. Increased mesothelial and capillary permeability.

As mentioned in the physiology section, normal pleural fluid is primarily a result of plasma from capillaries in the parietal pleura being drawn into the pleural cavity. As a result, those pleural effusions that are related to changes in pleural pressure balance bear similar characteristics to the plasma, also known as a transudative effusion. In contrast, those effusions related to impaired lymphatic drainage and increased permeability result in fluid that has increased protein and other cellular components. These effusions are called exudative pleural effusions. Laboratory differentiation of transudative and exudative effusions is described later.

### Clinical Features

Patients with a pleural effusion are often dyspneic upon presentation and may or may not complain of pleuritic chest pain. The dyspnea is relative to the size of the effusion as well as underlying respiratory disease. Other symptoms may accompany the dyspnea, but are often related to causes of the effusion (i.e., fever, weight loss, or weight gain).

### Diagnosis

Physical examination in a pleural effusion can often aid in diagnosis. Patients demonstrate decreased breath sounds in the areas of the effusion, with crackles heard at the border of the effusion and the lung. Dullness to percussion as well as decreased tactile fremitus is present.

The primary mode for definitively diagnosing a pleural effusion is chest x-ray. Fluid can best be demonstrated on chest x-ray in the lateral decubitus position. On lateral films, the fluid can be seen to be freely mobile or loculated. Ultrasound and CT of the chest can demonstrate effusions as well, but are not routinely employed for diagnosis. Ultrasound and CT are useful adjuncts in precisely locating loculated pleural effusions and guiding thoracentesis.

Once a pleural effusion has been diagnosed on radiography, a diagnostic thoracentesis is indicated. Thoracentesis is used as a diagnostic modality as a well as a therapeutic option. Thoracentesis will help to differentiate the likely etiology of a pleural effusion. Light et al. described diagnostic criteria that divided pleural effusions into two categories: transudative and exudative. The diagnosis of exudative effusions requires one of the following[13,14]:

1. Pleural fluid protein to serum protein greater than 0.5
2. Pleural fluid lactate dehydrogenase (LDH) to serum LDH greater than 0.6
3. Pleural fluid LDH greater than two-thirds of the upper limits of normal for serum LDH.

If a patient meets none of these criteria, they are diagnosed with a transudative effusion.

Visual examination of pleural fluid can assist in diagnosis. Normal pleural fluid is straw colored and clear. If the effusion is milky it may suggest a chylous effusion, parapneumonic effusion, or pseudochyle.

## Etiology

The etiology of pleural effusions are extensive, but as has been illustrated, is best divided into transudative and exudative etiologies. Table 20-2 lists common causes of pleural effusions.

**TABLE 20-2: Causes of Pleural Effusions**

| |
|---|
| Transudative |
| Congestive heart failure |
| Cirrhosis |
| Nephrotic syndrome |
| Pulmonary embolism |
| Exudative |
| Malignancy |
| Infection of lungs and surrounding tissue |
| Bacterial |
| Viral |
| Tuberculoid |
| Fungal |
| Chylous effusion |
| Hemothorax |
| Asbestosis |
| Sarcoidosis |
| Esophageal perforation |
| Pancreatitis |
| Collagen vascular diseases |
| Systemic lupus erythematosus |
| Rheumatoid arthritis |
| Sjogren's syndrome |
| Wegener's granulomatosis |
| Postsurgical |
| Drug induced |
| Amiodarone |
| Bromocriptine |
| Dantrolene |
| Nitrofurantoin |
| Pulmonary infarct |

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## Management

### TRANSUDATIVE EFFUSIONS

Transudative effusions are often caused by systemic disease that result in fluid overload, most commonly seen in congestive heart failure, cirrhosis, and nephrotic syndrome. However, pulmonary embolisms can also result in transudative effusions and high suspicion should be kept for those patients at risk for developing deep vein thromboses. For patients in fluid overload states, it causes a decrease in capillary oncotic pressure leading to increased pleural fluid production and overwhelmed ability to reabsorb the fluid. Pulmonary emboli cause increased venous pressure within the lungs and decrease the ability of the visceral pleura to absorb the fluid.

Conservative management consists of treating the underlying disease, along with diuretic therapy in fluid overload states, and often thoracentesis. Diuresis decreases the hypervolemic state that contributes to the increased pleural fluid production, and in most cases, rapidly resolves the effusion. Thoracentesis is reserved in patients with new onset effusions, unilateral or loculated effusions, febrile patients, and those with severe symptoms. For patients who fail conservative management, or are at end stage, pleurodesis can be employed. Often these patients are not good operative candidates and chemical pleurodesis is the treatment of choice.

### EXUDATIVE EFFUSIONS

Exudative effusions are often a result of a systemic process causing inflammation of the pleura. The primary goal in managing exudative effusions should be treating the underlying cause. Initial treatment of the effusion is accomplished through thoracentesis. Thoracentesis is used as a tool both for diagnosis as well as a therapeutic option. Often exudative effusions do reaccumulate and repeated thoracentesis is not recommended because it can result in pleural adhesions causing loculations as well as a risk of bacterial contamination. These patients should be managed with a tube thoracostomy in the short term. Long-term management for chronic effusions can be through chronic drainage with an indwelling chest tube, or through surgical management often with mechanical pleurodesis.

# PARAPNEUMONIC EFFUSIONS AND EMPYEMA THORACIS

## Definition

An empyema thoracis is a purulent pleural effusion. Infection can enter the pleural space through two primary ways[15]:

1. Direct inoculation from the surrounding viscera, most commonly the lung
2. Through the chest wall, seen in trauma or iatrogenic inoculation (commonly postsurgical).

Empyema thoracis is the final stage in the progression of stages of parapneumonic effusions. Parapneumonic effusions develop when a patient has an underlying pneumonia. These can be divided into uncomplicated and complicated. Generally, uncomplicated effusions are mild, contain no bacteria, and resolve with antibiotic treatment and resolution of the pneumonia. Complicated effusions can become loculated or infected progressing into an empyema requiring drainage. Parapneumonic effusions occur in 20 to 60 percent of hospitalized patients with bacterial pneumonias. Approximately 5 to 10 percent of these patients will progress to an empyema.[16]

Parapneumonic effusions progress through three stages. The first stage is called the exudative stage. The exudative stage consists of swelling of the pleural membrane with discharge of a pleural fluid that has a low LDH, normal glucose, and normal pH. This stage is reversible through appropriate antibiotic treatment of the pneumonia. If the pneumonia is untreated or incompletely treated, the effusion progresses into stage two or the fibrinopurulent stage. In this stage, bacteria invade the effusion, white blood cells enter the pleural space causing frank purulence on visual examination, and fibrin is diffusely deposited throughout the pleural cavity creating loculations. If appropriate antibiotics and drainage are not instituted, patients progress to the final stage, known as the organization stage. During this stage, fibroblasts grow into the fibrin sheets that have formed within the pleural space creating a thick collagen membrane known as a "peel." The peel entraps the pus within the pleural cavity and also compresses and entraps the lung.[15,16]

Several complications can arise as a result of an empyema. The fibrous tissue that forms the peel around the empyema can lead to a condition known as fibrothorax, which is discussed later. The extensive fibrosis can also invade the lungs and lead to significant pulmonary fibrosis as well. Also, the infection can track either laterally through the chest wall forming a fistula through the skin, known as an empyema necessitatis, or through the lung parenchyma into the bronchi, known as a bronchopleural fistula.[15]

## Clinical Features

Empyemas often present with a history of pleuritic pain, high fever, cough, dyspnea, and localized tenderness of the chest wall. These symptoms can develop acutely or can be present for weeks, depending on the stage of development of the parapneumonic effusion.

## Diagnosis

Pleural fluid obtained through thoracentesis will meet the criteria for an exudative effusion. Furthermore, a pleural fluid pH of 7.21 to 7.29 is the most sensitive criteria for diagnosis of an empyema. A low glucose, less than 50 mg/dL, and a high LDH, greater than 1000 IU/L, indicate an empyema.[16] Measuring the white blood cells within the fluid is of limited value because other noninfectious causes of exudative effusions can create an increased cell count such as pancreatitis. Culture of the pleural fluid is recommended; however, an organism is not isolated approximately 80 percent of the time.[15]

Determination of the stage of development at which parapneumonic effusion exists is difficult to assess clinically. Incorporation of ultrasound and CT has greatly increased the ability to identify patients who can be managed conservatively and those who will need drainage and possible decortication. Ultrasound can distinguish between pleural fluid, as well as definition of the acoustic makeup of a gathering effusion, pleural thickening, and parenchymal consolidation. CT scans are effective in determining if loculations exist within the effusion, if the lung is entrapped or involved with the effusion, and contrast CT scans will illuminate a fibrous peel.

## Conservative Management

Management of parapneumonic effusions and empyemas reflect the management of other pleural effusions. Initially, a thoracentesis is employed. For patients whose laboratory data are not indicative of a complicated pleural effusion, thoracentesis with appropriate antibiotics is often enough. However, patients with complicated effusions or with frank empyema require drainage. Simple tube thoracostomy is often ineffective and is no longer the standard of care. Placement of a pigtail catheter using image guidance is a common first approach. Patients who are considered candidates for catheter drainage are those without evidence of lung entrapment or obvious peel as evidenced by contrast enhanced CT. Once the catheter is in place, fibrinolytics are employed through the catheter to break up the fibrous capsule and aid in adequate drainage. Examples of fibrinolytics include streptokinase and tissue plasminogen activator. This approach can yield success rates of up to 70 to 80 percent for parapneumonic effusions and early-stage three patients.[16]

## Surgical Management

Failure of conservative management is defined as patients without improving symptoms and radiographic features after drainage and three doses of fibrinolytics.[16] If a patient

fails conservative management VATS can be employed to break up the fibrous adhesions, drain the pleural space, and assist in placement of chest tubes. Some authors argue for early thoracoscopy as a primary treatment. Studies have shown that early thoracoscopy has improved outcomes versus conservative management. For patients that are determined to be in the late portion of stage three, multiple areas of loculation, symptoms longer than 10 days, or parenchymal involvement decortication is indicated.

# CHYLOTHORAX

## Definition

Chylothorax is an accumulation of chyle in the pleural space caused by the disruption of the thoracic duct or one of its main divisions.

## Clinical Features

Patients often experience shortness of breath related to the effusion. These symptoms can be mild to severe depending on the acuity in onset and size of the effusion. Chylothorax can present as right, left, or bilateral effusions. The presentation is a result of the site of the lesion, and the anatomy of the thoracic duct as it ascends superiorly through the thorax.

The classic anatomical construction of the thoracic duct is present in only 65 percent of patients.[17] In the classic configuration, the thoracic duct forms in the midline from the cisterna chyli at the level of L1–L2. The cisterna chyli is a saccular confluence of lymphatic ducts from the lower body, hepatic lymphatics, and intestinal lymphatics. At the superior apex of the cisterna chyli, the thoracic duct is formed and begins its ascension. The thoracic duct enters the thorax through the aortic hiatus between T10 and T12, just to the right of the midline, alongside the right border of the aorta. At the level of T5–T6, it crosses the midline posterior to the aorta through the mediastinum and transcends superiorly along the left border of the esophagus. As the thoracic duct enters the neck, it arches 2 to 3 cm above the clavicle and travels laterally and anteriorly until it anastomoses with the venous system at the junction of the left internal jugular and subclavian veins. This anatomy can be important in determining the location of the leakage from the thoracic duct.[18]

## Physiology of Chyle

The primary function of the thoracic duct is to deliver chyle to the venous system. Chyle is composed primarily of lymph, but also contains electrolytes, proteins, enzymes, red blood cells, and a predominance of T lymphocytes. The lymph is primarily from the intestines and liver, and as a result is high in triglycerides (TGs), which gives chyle its characteristic milky appearance. Approximately 60 to 70 percent of fat that is absorbed in the intestines is transported in chyle and enters the bloodstream through the thoracic duct.[18] Up to 2.5 L of fluid can pass through the thoracic duct daily. Given that the primary component is nutritional fat, this amount varies—increasing after ingestion of fat and decreasing with starvation or diet low in long chain fatty acids. Given the high content of nutrients in chyle and substantial volume, which can be lost, a sustained chylothorax without nutrient replacement can lead to severe malnutrition. Of note, chyle is high in T lymphocytes and various immunoglobulins; therefore, the fluid that accumulates in the pleural space is generally sterile. However, this can render the patient immunocompromised due to decrease in circulating lymphocytes, which can further lead to morbidity.

## Causes of Chylothorax

There are congenital, traumatic, neoplastic, and miscellaneous causes of chylothoraces. Congenital chylothorax is rare; however, it is the leading cause of pleural effusions in the newborn. Congenital causes include anatomical defects in the thoracic duct and its tributaries. Birth trauma has also been identified as an etiology. Traumatic chylothorax can occur after most types of blunt or penetrating trauma. Operative trauma is a common cause of traumatic chylothorax. Almost every thoracic surgical procedure has been reported as a cause of chylothorax. With traumatic chylothorax, the insult to the thoracic duct can be minor. Simple abrupt hyperextension of the spine can cause a rupture of the thoracic duct. Importantly, in 1971, Beesone et al.[19] argued that chylothorax caused by nonsurgical trauma should cause concern for underlying malignancy and warrants investigation. Neoplastic causes of chylothorax include lymphoma, lymphosarcoma, or primary lung cancer. The most commonly reported mechanisms of chylothorax from a neoplasm are direct invasion of the thoracic duct causing distension and rupture of tributaries, or compression and subsequent erosion of the duct. Miscellaneous causes include lymphangioleiomyomatosis, which is seen in women of reproductive age, infections, filariasis, cirrhosis of the liver, and tuberculosis.

## Diagnosis

The majority of the time chyle is a milky odorless fluid, and visual inspection of the fluid is often considered helpful in diagnosis. However, it is important to remember that chylous effusions can lose their milky appearance if the patient has been fasting, and further confusion can arise if the thoracic duct leak was caused by trauma, leading to bloody effusions. Furthermore, it is important to keep in mind mimics of chylothorax. Pseudochylothorax often has a similar milky appearance and should be distinguished from chylothorax. Pseudochyle is associated with chronic pleural effusions, commonly seen in malignant tumors and infection, and it

is milky because of the presence of cholesterol in the fluid. Laboratory studies are commonly used to differentiate chylous effusions from other etiologies. The most common laboratory diagnosis is based on TG levels.[18] An effusion with a TG level greater than 110 mg/dL has been shown to have a less than 1 percent chance to be a nonchylous effusion. An effusion with a TG level of less than 50 mg/dL is chylous less than 5 percent of the time.[20] Further confirmation can be obtained by examining the cholesterol to TG ratio. Chylous effusions generally have a ratio of less than 1, whereas nonchylous effusions have a ratio of greater than 1. If the diagnosis is unclear after these laboratory studies, the gold standard for diagnosing a chylothorax is the demonstration of chylomicrons in the effusion. This is accomplished by lipoprotein analysis. A lipoprotein analysis is used to demonstrate chylomicrons in the effusion, which are considered pathognomonic for chylothorax.

## Medical Management

Unfortunately, there is no clear pathway for patients who should be treated conservatively versus those who will require surgery. Often this is due to the diverse presentations and etiologies of chylothorax. However, it should be stressed that treatment of a chylothorax is necessary, given the severity of nutritional deficiencies that can develop with a sustained leak. Therapeutic options include treating the underlying cause, conservative medical management, and surgical management. Treating the underlying cause, as with neoplastic etiologies, can help to alleviate the chylothorax, but often requires additional therapy.

The pillars of medical management involve drainage of the effusion, nutritional supplementation, and attempts to reduce/stop the flow of chyle. Drainage is accomplished by tube thoracostomy. Careful attention should be paid to the amount of drainage, as it is used as an indication for surgery, which is detailed later. Furthermore, chronic chest tube drainage of chyle can become obstructed due to the fatty nature of chyle, requiring multiple thoracostamies. Nutritional supplementation, historically, consisted of either oral supplementation with medium chain TGs (given their preponderance for absorption in the portal circulation) or nothing by mouth (NPO) with total parental nutrition (TPN). Studies have indicated that any oral intake increases chyle flow, regardless of its composition, and the NPO/TPN therapy has shown improved closure rates. With either therapeutic option, it is important to monitor the patient's nutritional status and adequately replete nutritional deficiencies because malnutrition can lead to increased morbidity and mortality. Finally, to stop chylous flow, various attempts at ensuring complete expansion of the lung, leading to compression of the lesion, were instituted in the past. Chemical pleurodesis was the most common option, but positive-pressure ventilation and inhaled nitrous have also been reported. Excitingly, beginning with the first case report in 1990, a new therapy has been reported in the literature.[21] The use of somatostatin, or its synthetic analogue octreotide, has increasingly been described as a conservative option. The mechanism of action is unclear, but it has been hypothesized that the peptide decreases the flow of chyle through the thoracic duct due to its inhibitory effects on intestinal absorption. Currently, there have been no randomized trials evaluating its efficacy, but the reported data are encouraging and should be considered as an option. Imaging via invasive lymphangiography can be diagnostic to determine not only the site of the chylous leak, but also if anatomic anomalies are present. This could help in operative planning. Therapeutically, the contrast used has been known to help seal the chyle leak in up to 50 percent of cases.

A trial of medical management should be no longer than 7 days, but surgery may be indicated prior to this timeline, as is indicated later. If the patient responds to therapy, objectively measured by low chest tube output (<250 mL/24 h), evacuation of the pleural space as evidenced by radiographic findings, and the patient has improved symptomatically, a trial of regular diet can be instituted. If the chest tube output remains low and no evidence of reaccumulation of a chylous effusion is present, the chest tube can be pulled.

## Surgical Management

In 1973, Selle et al.[22] reported a pathway that has served as a general guideline for surgical indications for chylothorax. They are the following:

1. Idiopathic cases in the neonate usually respond well to thoracentesis.
2. Nontraumatic chylothorax, exclusive of the neonatal group, usually suggests a widespread fatal illness, and operative intervention is usually ineffective and should, therefore, be avoided.
3. In cases resulting from trauma, an initial trial of nonoperative management is indicated. Transthoracic ligation of the duct is indicated when
   a. The average daily chyle loss has exceeded 1500 mL/day in adults or 100 mL per year of age in children for a 5-day period.
   b. The chyle flow has not diminished while approaching 7-day duration.
   c. Nutritional complications appear imminent.

If patients do require surgical management, the current approach to chylothorax is thoracic duct ligation, introduced by Lampson in 1948.[18] Ligation of the thoracic duct should occur just above the diaphragm, in the right chest, as the thoracic duct enters the thorax. Approximately 75 percent of patients have a single thoracic duct that enters the right chest, and this has been proven to be the most effective therapy.[17,22] There are several approaches to ligate the thoracic duct. These include direct ligation of the thoracic duct, mass ligation of the thoracic duct, thoracoscopic ligation, application of fibrin glue, pleuroperitoneal shunt, and pleurectomy.

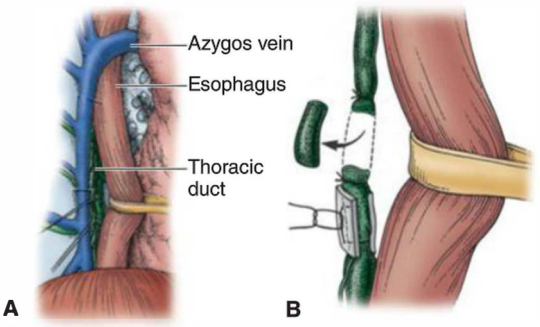



**FIGURE 20-1** **A.** Surgical anatomy of the thoracic duct and **B.** mass ligation of the thoracic duct with Teflon Pledgets. (Reproduced with permission from Miller JI. Anatomy of the thoracic duct and chylothorax. In: Shields TW, LoCicero J, Ponn RB (eds). *General Thoracic Surgery*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2000;747–756. Copyright Lippincott Williams & Wilkins.)

Direct visualization of the chyle leak intraoperatively can be attempted by giving the patient a fatty oral substance, such as olive oil, through the nasogastric tube 2 to 3 h prior to the operation. This will create a milky white flow through the thoracic duct that can aide in visualizing the lesion. Another option includes administering 1 percent aqueous solution of Evans blue dye in the patient's leg. The dye will appear in about 5 min and can last up to 12 min.[18]

There are two postsurgical chylothoraces that require special mention. Chylothorax after esophagectomy has been reported as a complication between 2 and 4 percent. This is generally thought to be related to the close anatomical proximity that the thoracic duct shares with the esophagus. For these patients, medical management has not proven effective and surgical management is the optimal treatment. Conversely, pulmonary resections have a significantly lower reported rate of chylothorax and often respond well to medical management. Finally, it should be emphasized that any thoracic duct lesion that is directly visualized intraoperatively should be repaired prior to closure.[18]

Figure 20-1 depicts surgical anatomy of the thoracic duct as seen via thoracotomy.

# FIBROTHORAX

## Definition

Fibrothorax is the development of a fibrous adhesion between the pleura. Fibrothorax can have multiple etiologies, but the underlying pathophysiology is similar.

## Clinical Features

Chronic pleural effusions, transudative or exudative, result in inflammatory responses by the mesothelium of the pleura. This response results in the deposition of a fibrinous layer of collagen matrix around the effusion. The matrix encapsulates the effusion forming a membrane that separates the effusion from the rest of the pleural space. This membrane can be thin, as seen in transudative effusions, or a thick peel as seen in empyemas. The membrane adheres to the pleura; however, the pleura itself is usually not invested in the matrix, resulting in a discrete extrapulmonary mass. The pleura can become invested if the initial effusion was an extension from a parenchymal process. As the fibrinous membrane evolves, it becomes adherent to the pleura lining the chest wall and diaphragm and can impair their movement, as well as create a mass effect against the lung, preventing it from expanding properly. Consequently, patients often present with dyspnea on exertion that worsens over time. Cough and fatigue are often present, and worsen with the increased involvement of the chest wall and diaphragm.[23,24]

## Diagnosis

Physical examination demonstrates decreased breath sounds over the affected area as well as dullness to percussion. The intercostal spaces surrounding the fibrothorax are often decreased, leading to decreased ability to fully expand the chest wall during inspiration. Pulmonary function tests demonstrate a restrictive ventilatory defect due to chest wall involvement and decreased lung expansion.[24]

CT is the diagnostic modality that best visualizes fibrothorax. The scans confirm the extrapulmonary location of the fibrothorax and can efficiently demonstrate the size and characteristics of the mass. Furthermore, the lungs can be visualized to determine if there is parenchymal involvement as well as inspection for the underlying etiology. Chest x-ray demonstrates radioapaque densities generally present in the diaphragmatic region with blunting of the costodiaphragmatic angle. The hemithorax is often reduced in size and the mediastinum shifted toward the affected side.

## Management

Intervention for fibrothorax is indicated in patients with symptomatic disease, ventilatory defects, or those with significant pleural involvement. Conservative management primarily consists of attempts at draining the pleural effusion either through thoracentesis or tube thoracostomy. The efficacy of these techniques depends on the maturation of the fibrinous peel. The patient should be assessed to determine if their symptoms have improved, and if the effusion has decreased on radiography. If not, surgical management should be considered.

The classic management for fibrothorax is decortication. Decortication is indicated if a patient has failed conservative management, the lung is determined to be more than 50 percent collapsed, or the apex is collapsed. Decortication consists of dissecting the peel off the underlying pleura and

suction evacuation of the pleural cavity. Timing of decortication depends on the underlying etiology; for example, fibrothorax secondary to hemothorax should be performed at least 6 weeks following the insult to allow for maturation of the peel.[23,24]

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## BENIGN PLEURAL DISORDERS BOARD REVIEW QUESTIONS (CHAPTER 20)

1. Which of the following is true regarding pleural anatomy?
   A. The visceral pleura does not invest the fissures.
   B. Venous drainage from the visceral pleura is through bronchial veins.
   C. The visceral pleural is not innervated by the somatic nervous system.
   D. Venous drainage from the parietal pleura is through the pulmonary veins.
   E. Lymph drainage from the parietal pleura is through the thoracic duct.

2. Which is true for pneumothorax?
   A. Cigarette smoking is not a risk factor for PSP.
   B. The most common pulmonary disease associated with SSP is cystic fibrosis.
   C. The incidence of secondary pneumothorax is higher than primary pneumothorax in males.
   D. Pneumothorax occurs in up to 50 percent of thoracic trauma patients.
   E. In-hospital pneumothorax occurs most commonly from positive-pressure ventilation.

3. Which of the following is not an indication for surgical treatment of pneumothorax?
   A. Incomplete lung expansion
   B. Bilateral spontaneous pneumothorax
   C. Persistent air leak
   D. Recurrent pneumothorax
   E. Large air leak

4. Which is correct regarding empyema?
   A. 5 to 10 percent of patients with a parapneumonic effusion will develop empyema.
   B. The fibrinopurulent stage is reversible with appropriate antibiotic therapy.
   C. Pleural fluid has a high LDH and low glucose in the exudative stage.
   D. The presence of white blood cells in the pleural fluid is pathognomonic of empyema.
   E. Over 90 percent of patients with have a positive pleural fluid culture.

5. Which is true for the treatment of chylothorax?
   A. Neonates should have prompt placement of a chest tube to prevent fibrothorax.
   B. Long-term TPN is the preferred strategy for chylothorax after esophagectomy.
   C. Surgery is indicated when chyle losses exceed 1500 mL/day.
   D. Ligation of the thoracic duct is best performed via left thoracotomy at the level of the diaphragm.
   E. Chylothorax after pulmonary resection requires prompt reoperation.

## ANSWERS

1. **Answer: C.** The visceral pleura is not innervated by the somatic nervous system. It does invest the fissures and venous drainage is through the pulmonary veins. Venous drainage of the parietal pleura occurs through companion veins to the arterial supply, and lymphatic drainage is through the local and regional lymph node systems.
2. **Answer: D.** Up to 50 percent of patients with thoracic trauma will have an associated pneumothorax. Cigarette smoking is an important risk factor for pneumothorax. The most common underlying pulmonary disease is emphysema. Primary pneumothorax is more common than secondary pneumothorax in males. In-hospital pneumothorax is most commonly due to percutaneous lung biopsy.
3. **Answer: E.** If the lung is well-expanded and the patient is otherwise stable, the presence of a large air leak is not an indication for surgical treatment.
4. **Answer: A.** Up to 10 percent of patients with a parapneumonic effusion will go on to develop empyema. The exudative phase is reversible with appropriate antibiotics. High LDH and low glucose is characteristic of the chronic phase. The presence of white blood cells is not pathognomonic of empyema. Up to 80 percent of patients will have a negative pleural fluid culture in the setting of empyema.
5. **Answer: C.** When chyle losses exceed 1500 mL/day, conservative therapy is unlikely to resolve the chylothorax and surgery is indicated. Neonatal chylothorax is treated with repetitive thoracentesis. Chylothorax after esophagectomy requires surgery, whereas chylothorax after pulmonary resection should be initially treated with medical management. About 75 percent of patients have a single thoracic duct entering the right chest at the diaphragm; therefore, ligation is best performed via right thoracotomy.

21

# Benign and Malignant Pleural Tumors

*Siva Raja*
*Carol F. Farver*
*Sudish C. Murthy*
*David Mason*

**KEY CONCEPTS**

- Epidemiology
  - Pleural tumors are a small but significant subset of thoracic malignancies. The majority of pleural tumors tend to be malignant and mesothelioma is the most common diagnosis. Most patients have had environmental exposure to asbestos.
- Pathophysiology
  - Pleural tumors are generally characterized as benign or malignant. Benign tumors are usually slow growing and do not cause symptoms until they exert mass effect, or in the case of MPM, when they cause pain by tumor invasion or dyspnea secondary to pleural effusion.
- Diagnosis/clinical features
  - Many pleural-based tumors are diagnosed incidentally on imaging performed for unrelated reasons. The primary radiographic evaluation consists of CXR and CT scan. Once the pleural-based lesions have been identified, tissue diagnosis is obtained via image-guided core-needle biopsy or through thoracoscopic biopsy. When symptoms are present, they are most commonly chest wall pain from tumor invasion or dyspnea from restriction or cough.
- Treatment
  - Benign tumors of the pleura are followed with serial imaging or resected. Treatment options for MPM are varied and range from palliation of symptoms to radical surgery within a multimodality regimen.
- Prognosis
  - The prognosis for benign lesions of the pleura is excellent and recurrences are rare after complete resection. MPM, however, is often advanced at presentation and prognosis is poor. However, early-stage patients with epithelioid histology and negative resection margins have promising long-term survival.

## INTRODUCTION

The diagnosis and treatment of pleural diseases was a formidable task for practitioners of ancient and medieval medicine as most maladies of the thoracic cavity proved to be rapidly and universally fatal. The development of general anesthesia, thoracic imaging, and closed suction drains has greatly facilitated the diagnosis and treatment of pleural disease, including primary tumors of the pleura.

## PLEURAL ANATOMY

The pleura refers to a continuous mesothelial tissue layer of mesenchymal origin that lines the chest cavity and blankets thoracic structures.[1,2] Standard nomenclature differentiates the parietal pleura, which covers the chest wall, mediastinum, and diaphragm, from the visceral pleura, which invests the lung parenchyma. The hilum of the lung and the inferior pulmonary ligament serve as the anatomic interfaces

between these two layers. Blood supply and lymphatic drainage follow that of structures—parietal pleura supplied by intercostal, internal mammary, superior phrenic, and anterior mediastinal arcades. Lymphatics drain to intercostal, mediastinal, and phrenic lymph nodes. Communications across the diaphragm and chest apex link the thorax to the peritoneal cavity and ipsilateral axillary lymph nodes respectively. The visceral pleura contain both a pulmonary and a bronchial blood supply but drains solely into the pulmonary venous circulation. Visceral pleural lymphatics drain to mediastinal lymph nodes. Autonomic and somatic fibers innervate the pleura. The visceral pleura carry autonomic fibers only. Pain, carried through somatic routes, is generated from parietal pleural inflammation, such as by direct tumor invasion or local irritation.

## EVALUATION OF PLEURAL-BASED ABNORMALITY

The evaluation of a patient with pleural pathology begins with a thorough history and physical examination (Fig. 21-1). Identification of environmental exposures, particularly asbestos, can provide important insight to the etiology. Other risk factors for pleural disease such as a known prior malignancy or a history of tuberculosis should be identified. A history of cough or fever suggests infectious etiology, whereas a history of weight loss and chest pain portends a malignant diagnosis. Surprisingly, many pleural tumors are diagnosed incidentally on radiographic examinations performed for screening of unrelated diseases.

Dyspnea and chest pain are the most common presenting symptoms in patients with pleural tumors. For symptomatic patients, the plain chest radiograph (CXR) is typically the first diagnostic test performed, although this is neither sensitive nor specific. Common CXR findings are pleural plaques and effusions. Most CXR findings lead to computed tomography (CT), or possibly, magnetic resonance imaging (MRI). Chest CT scans are relatively inexpensive and provide excellent high-resolution anatomic information. Due to this, chest CT scan is the most commonly used noninvasive modality to differentiate pleural from parenchymal disease. MRI is more expensive, relatively difficult to obtain at most centers, and confounded by motion artifact, but it can add information regarding mediastinal, vascular, chest wall, or diaphragmatic invasion.

Once the presence of a suspicious pleural lesion is confirmed, tissue diagnosis is typically obtained for definitive diagnosis. This can be accomplished by cytologic examination of fluid obtained via thoracentesis of a pleural effusion or image-guided core-needle aspiration of a pleural-based mass. Should these tests prove nondiagnostic, a single-port video-assisted thoracic surgery (VATS) pleural biopsy is indicated. In addition to clarifying the diagnosis, VATS can both confirm the lesion as pleural-based and facilitate pleurodesis should this be appropriate. Care should be taken to plan the biopsy incision within the line of a possible future thoracotomy so that the site can be excised at the time of definitive surgery and limit potential port site implants (especially for mesothelioma).

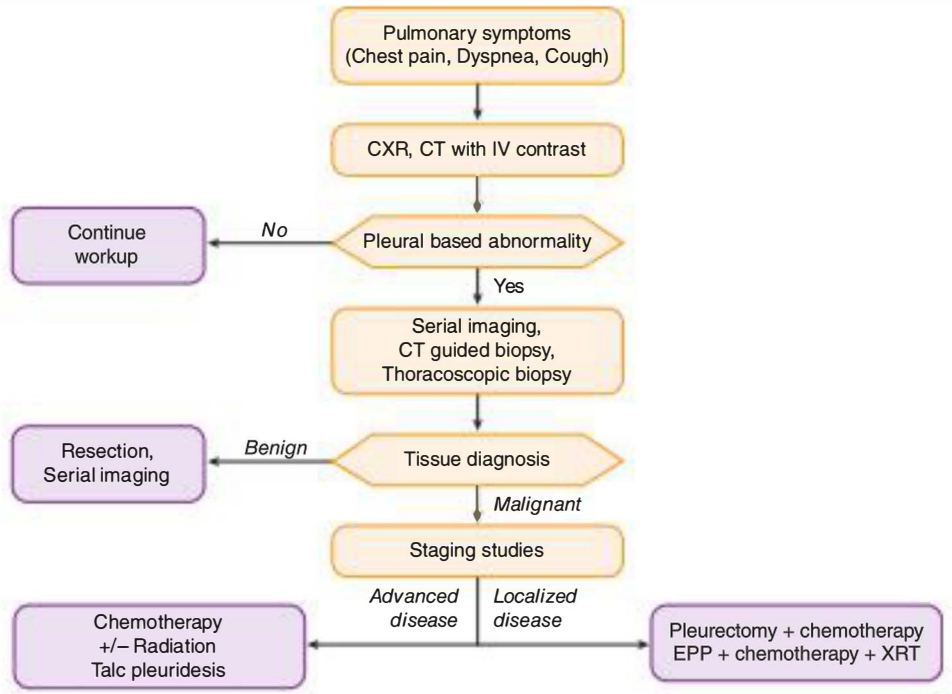



**FIGURE 21-1** Decision algorithm for evaluating pleural tumors.

## BENIGN TUMORS OF THE PLEURA

Benign lesions of the pleura are relatively common and usually detected incidentally. These include lipomas, plaques, and pleural thickening. Rounded atelectasis is often misdiagnosed as a pleural lesion. The most common presenting symptom, if any are present at all, is dyspnea secondary to parenchymal compression. Chest pain is unusual for benign tumors.

### Pleural Lipomas

Pleural lipomas are benign, slow-growing tumors that arise from fat cells present in the pleural lining. They are well circumscribed, small tumors but can grow to large sizes leading to compressive symptoms. They have a characteristic low density, homogenous appearance on CT imaging.[3] Malignant transformation of lipomas is extremely rare. Pleural lipomas can typically be differentiated from their malignant counterpart, liposarcoma, which tends to have a heterogeneous appearance on imaging.

When the adipose tissue of a suspected lipoma consists of fetal brown fat, it is referred to as a hibernoma.[4] These lesions are distinguished on pathology by increased vascularity and immature fat cells with multiloculated c ytoplasm. Some reports have also suggested that the skin over these lesions is warm due to the heat generated via an uncoupling of the mitochondrial electron transport. Small lipomas can be followed with serial imaging, whereas larger lipomas are typically excised for cure.

### Pleural Plaques and Diffuse Pleural Thickening

Although not technically tumors, pleural plaques and pleural thickening represent a reaction to environmental irritants and can mimic malignancy.[5] Plaques are reactive fibrosis, which are typically located on the chest wall or diaphragm and incited by asbestos exposure. Calcification of these plaques is pathognomonic for asbestosis (Fig. 21-2). Diffuse pleural thickening is a more extensive process that can involve circumferential encasement of lung parenchyma with accompanying pleural symphysis.[6] Etiology includes diffuse inflammatory conditions, radiation exposure, infection (empyema), and idiosyncratic medication response (bromocriptine and methysergide).

### Rounded Atelectasis

Rounded atelectasis can be seen in the setting of asbestos exposure as well as in association with other inflammatory conditions. It is thought to be initiated in the setting of an exudative pleural effusion that ultimately leads to thickening, contraction, and fusion to an adjacent fold of pleura.[7] This process creates atelectasis of the dependent lung parenchyma to produce a rounded peripheral nodule. It is a silent condition whose diagnosis is usually made incidentally during the workup of a solitary pulmonary nodule or a pleural-based mass. Clues on radiographic imaging can help differentiate rounded atelectasis from other lesions. CXR characteristics include volume loss of the ipsilateral lung, peripheral location, presence of pleural thickening adjacent to the lesion, and the pathognomonic "comet tail" finding, a convergence of the pulmonary vasculature as it enters the hilar side of atelectatic lung. The "comet tail" is best seen on CT scan. As rounded atelectasis is usually metabolically inactive, positron emission tomography (PET) scan is sometimes helpful in ruling out a malignant diagnosis.[7]

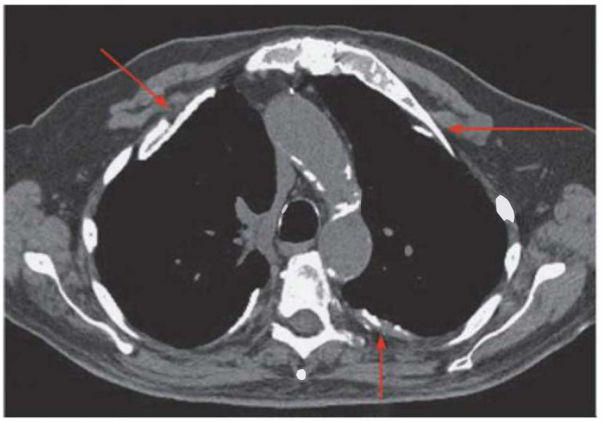


**FIGURE 21-2** CT scan of pleural plaque with calcification (arrow).

## MALIGNANT TUMORS OF THE PLEURA

### Solitary Fibrous Tumors of the Pleura

Although most solitary tumors of the pleura (SFTP) are composed of benign-appearing cells, they can nonetheless undergo malignant transformation and cannot simply be classified as "benign" lesions.[8] SFTP are most commonly discovered as incidental radiographic findings. They can grow very large and cause chest pain, cough, and dyspnea from mass effect. Although unusual, malignant transformation is evidenced by rapid growth or even distant metastasis. Occasionally, SFTP are secretory and the liberation of factors such as insulin-like growth factor 2 (IGF2) can create hypoglycemia.[9] SFTP are also associated with pulmonary osteoarthropathy.

Chest CT scan is typically adequate for diagnosis of SFTP although occasionally MRI or PET scanning can provide useful diagnostic and anatomic information. SFTP has pathologic correlates in the kidney, cervix, meninges, thigh, pelvic fossa, retroperitoneal, and serosal surfaces. In earlier literature, this entity was referred to as "localized mesothelioma" or "fibrous mesothelioma." However, it has now

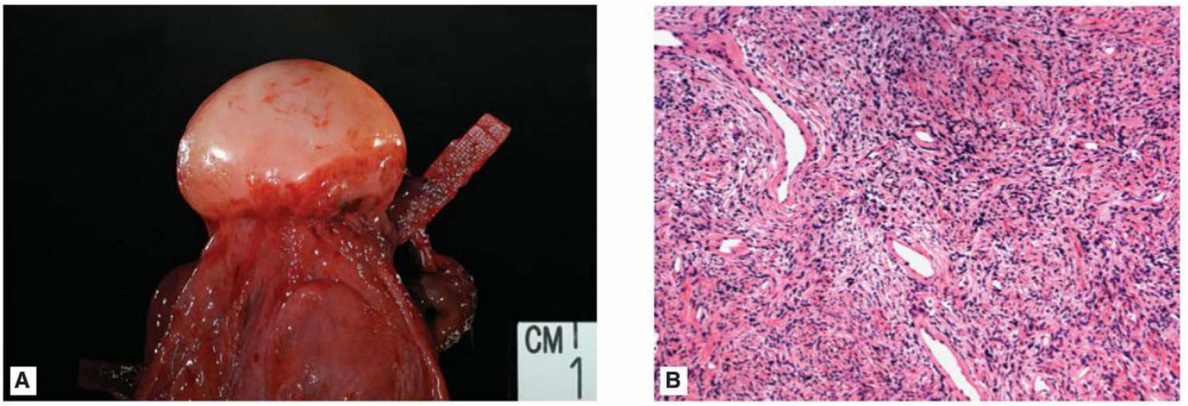



**FIGURE 21-3** Solitary fibrous tumor of the pleura: Gross image (**A**), H&E stained section (**B**).

become clear that these tumors arise from pleural mesenchymal cells most closely resembling pericytes (a dendritic-like smooth muscle cell) rather than mesothelium. The majority of SFTP arise from the visceral pleural layer, presenting as pedunculated lesions (Fig. 21-3A).

The histologic features include bipolar spindle cells with varying areas of cellularity, often with small vessels and perivascular hyalinization (Fig. 21-3B). These tumors stain for CD34 (a vascular marker) and are distinguished from sarcomatoid mesotheliomas by absence of staining for cytokeratin and calretinin.[10,11] There are no definitive histologic features that discriminate benign from malignant SFTP. However, tumors with a mitotic rate greater than 4 mitoses per 10 high-power fields and greater than 10 cm in size are more likely to recur locally. The treatment of SFTP is surgical resection (Fig. 21-3A). Adjuvant therapy is not typically warranted, particularly if the lesion is completely resected.

## Malignant Mesothelioma

### EPIDEMIOLOGY

Malignant pleural mesothelioma (MPM) is a rare thoracic malignancy, directly linked to asbestos exposure. The incidence of MPM remains low at about 2000 to 3000 new cases[12] per year compared with lung cancer that has over 160,000 new cases per year, but has gradually increased over the past 5 decades. Although the use of asbestos dates back to thousands of years, it became widespread with increased industrialization as it was used as a form of insulation in many industries. These include construction, shipbuilding, pipefitting, and car brake assembly, due to its properties of light weight, low cost, and high heat resistance. Asbestos is a natural silicate mineral that can be categorized as serpentine and amphibole. Serpentine asbestos is composed of spiral fibers compared with amphibole asbestos whose fibers are linear and needle-like. This shape of amphibole is believed to cause chronic irritation that may lead to malignant transformation of the pleura.

The link between asbestos and MPM was first noted in asbestos mine workers dating back to the 1940s.[13,14] The vast majority of patients diagnosed with MPM have a documented link to asbestos exposure. Other less common etiologies include high-dose radiation exposure as well as simian virus infection.[12] However, asbestos remains the most clearly established causative agent. The development of mesothelioma typically trails exposure by 2 to 3 decades.

### PATHOLOGY

MPM arises from the mesothelial lining of the pleura and is often radiographically characterized by diffuse pleural thickening (Figs. 21-4 and 21-5). They are typically found as two major histologic variants: epithelioid type and sarcomatoid types (Figs. 21-6A and 21-6B). Some tumors have characteristics of both and are considered biphasic or mixed. In the workup, MPM must be differentiated from pleural dissemination of non–small cell lung cancer (especially adenocarcinoma). Although it is difficult to distinguish between the two with routine histologic examination, antibodies specific to mesothelioma have greatly increased diagnostic accuracy. Specially, antibodies to calretinin, Wilms tumor-1 (WT-1), and cytokeratin 5/6[15] are strongly positive in malignant epithelioid mesothelioma but are negative in adenocarcinoma.

Recent advances in cancer genetics have identified several pathways that appear to be in MPM. Numerous tumor suppressor genes including p16, p14, and p53 are affected, and aberrant expression of growth factors/receptors such as transforming growth factor-α (TGF-α), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and hepatocyte growth factor (HGF) are identified.[16] However, the molecular mechanism by which asbestos induces MPM has not been determined.

### CLINICAL PRESENTATION

The most common presenting symptom of MPM is dyspnea, and it is typically caused by pleural effusion. On physical examination, dullness to percussion is found on the affected

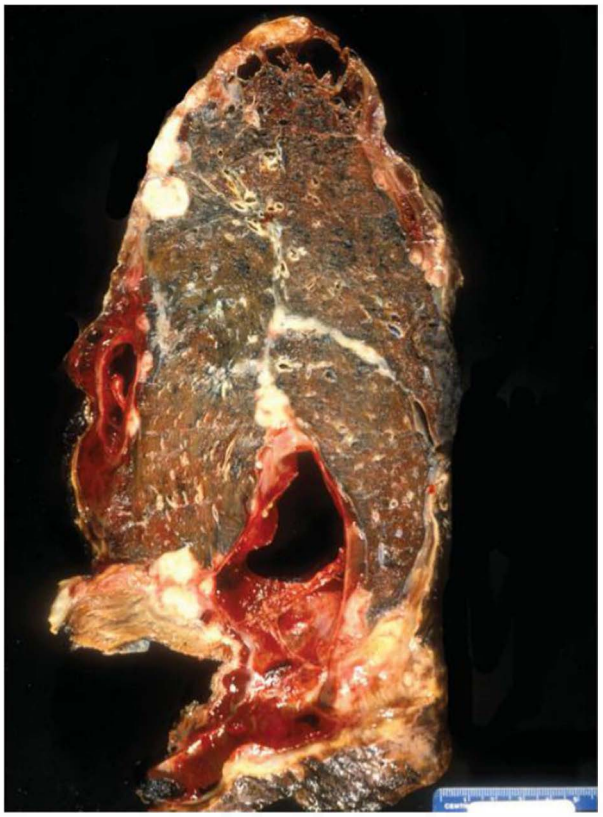


FIGURE 21-4 Sagittal plane image of malignant pleural mesothelioma from an extrapleural pneumonectomy specimen.

hemithorax. Chest pain is also common due to tumor involvement of the parietal pleura or chest wall. Weight loss is an ominous and late sign of disease along with generalized malaise and failure to thrive. No specific laboratory studies are diagnostic of MPM although thrombocytosis can be present.[17]

## RADIOGRAPHIC EVALUATION AND CLINICAL STAGING

Chest CT is the most commonly used modality for the evaluation of MPM. Early-stage tumors present with focal areas of pleural thickening and may be accompanied by pleural effusions. (Fig. 21-5). In later stages, MPM presents as large masses or circumferential tumors that completely encase the lung and invade mediastinal structures. PET scanning is used to screen for metastatic disease that is common,[18] although it is not as helpful for detecting locoregional and lymph node involvement.[19] MRI can be used to evaluate transdiaphragmatic invasion if radical surgery is being considered.

## CLINICAL-PATHOLOGIC STAGING

Clinical staging occurs after definitive tissue diagnosis. This can be obtained by cytology obtained from a pleural effusion or via a single-port thoracoscopy. Again, this port should be placed in line of a potential future thoracotomy if the patient appears to be a multimodality therapy candidate. The staging system for MPM has been defined in the 7th edition of the American Joint Commission on Cancer (AJCC) staging manual using standardized T, N, and M designations. PET scanning is useful in clinical staging although its sensitivity for T and N staging has been questioned. As mediastinal lymph node disease portends poor prognosis, cervical mediastinoscopy is recommended for patients who are candidates for aggressive multimodality therapy. Brain imaging should be performed to rule out metastatic disease. Although some centers recommend peritoneal lavage to rule out transdiaphragmatic spread, this is not routine for most centers. Due to the inherent inaccuracy of T and N staging based on CT and PET imaging, clinical staging of mesothelioma is imperfect. Definitive staging can only be obtained after radical surgical resection and evaluation of the entire pathologic specimen. Transdiaphragmatic and extensive chest wall invasion are usually contraindications to radical surgery.

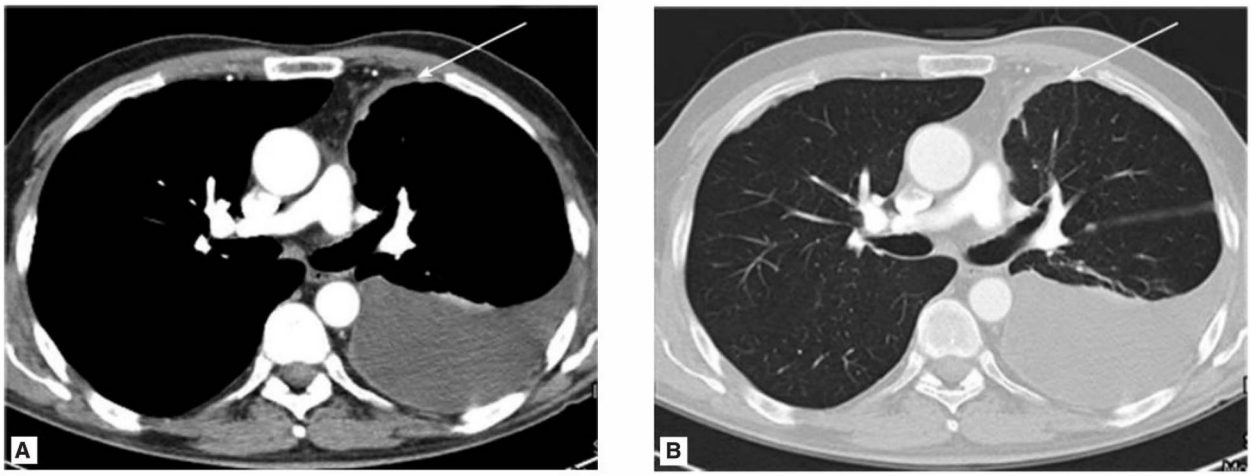



FIGURE 21-5 Malignant pleural effusion is seen posteriorly. Arrow shows pleural thickening.

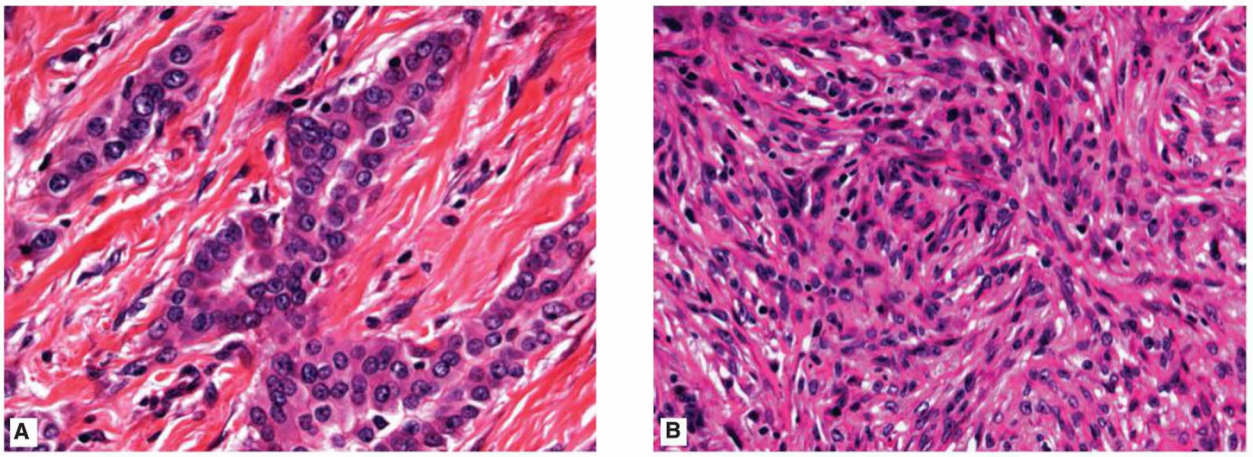



FIGURE 21-6 Malignant pleural mesothelioma. **A.** Epithelioid type. **B.** Sarcomatoid type.

### TREATMENT

***Medical.*** Treatment modalities depend on the patient's age, performance status, and disease stage at presentation. As most patients present with advanced disease, the mainstay of therapy for most is chemotherapy. Life expectancy in advanced disease is short and prolongation of life with chemotherapy is limited. The 5-year overall survival for this group of patients is about 15 percent. Traditional chemotherapy had included monotherapy with a wide variety of agents. Recently, a phase III trial testing a doublet using pemetrexed and cisplatin has shown efficacy. There was an overall 23 percent risk reduction for this cocktail compared with cisplatin monotherapy and the median survival was increased from 9.3 to 12.1 months.[20] Thus, the current recommendations for chemotherapy for mesothelioma include cisplatin and an antifolate agent such as pemetrexed or raltitrexed.

Radiation therapy is not indicated as primary therapy given the large treatment field required and associated toxicities. Instead, radiotherapy is used as an adjunct after radical surgery (extrapleural pneumonectomy, EPP) in multimodality therapy treatment protocols, or for palliation of pain.

Intraoperative photodynamic therapy (PDT) is a less common therapy. PDT uses laser light to activate a photosensitizer loaded into tumor cells to cause cytotoxicity and apoptosis. This treatment also stimulates a vigorous antitumor immune response.[21] It has been argued that because the cytotoxic effect penetrates several millimeters in depth on surfaces such as the visceral pleura and the diaphragm, radical resection is unnecessary.[22] Although there have been no studies that have clearly shown a benefit, future studies in early-stage patients may yet validate this treatment modality.

***Surgical.*** Although still debated, surgical therapy appears to offer improved survival in highly selected patients with MPM. Unfortunately, only a small fraction of patients who present with MPM are candidates for surgical resection. Due to the nature of MPM, "complete" resection is improbable and the goal of surgery is as a cytoreductant. Adjuvant therapies are aimed at eradicating residual microscopic disease postoperatively.

The main surgical options include EPP or pleurectomy/decortication (P/D). P/D is preferred for patients with disease primarily limited to the parietal pleura, where the removal of the parietal pleura provides significant tumor cytoreduction. When more extensive disease is present, EPP may yield maximal cytoreduction. The outcomes from both surgeries are comparable when adjusted for stage.[23] The results of that study also suggested that P/D might be preferred for stage I disease and EPP for stage II disease.

Most studies have focused on surgery with adjuvant therapy rather than surgery as monotherapy. A report of 183 patients who underwent EPP followed by chemotherapy (carboplatin and paclitaxel) and radiation (30 Gy) demonstrated a 2- and 5-year survival of 38 and 15 percent, respectively, as well as a 3.8-percent per-operative mortality.[24] Nodal metastasis, sarcomatoid subtype, and positive resection margins were risks for poor survival. In the absence of these risk factors, a 5-year survival of 45 percent and a median survival of 51 months were observed. Another recent study examining induction chemotherapy followed by EPP and hemithoracic radiation (>50 Gy) also showed similar survival.[25,26] Specifically, a 75-percent survival in ypT1-2NO patients and an overall 5-year survival for node negative patients of 53 percent were demonstrated. Intracavitary hyperthermic chemotherapy (ICHC) has been tested but has not shown a clear benefit.

## OTHER PLEURAL MALIGNANCIES

### Lymphoma

Pleural involvement of systemic lymphoma is common. However, there have been reports of a lymphoma limited to the pleura (primary pleural lymphomas). In a recent

single-institution study, just 6 of 34 patients with pleural involvement of lymphoma were found to be primary.[27] Diagnosis was predominantly made with pleural needle biopsy and the most common subtypes were diffuse large B-cell lymphoma followed by follicular lymphoma.

## Pleuropulmonary Synovial Sarcoma

Synovial sarcoma occurs predominantly on para-articular surfaces. Primary presentation in the lung, pleura, and chest wall is exceedingly rare.[28] The diagnosis of pleuropulmonary synovial sarcoma (PPSS) initially requires the exclusion of an extrathoracic primary. On chest CT scan, these lesions are large with well-circumscribed borders and heterogeneous enhancement due to central necrosis and hemorrhage. Similar findings are seen on MRI. Unfortunately, radiographic imaging does not help differentiate this lesion from other fast-growing lesions of the pleura and lung. Most synovial sarcomas have a translocation and fusion of the SYT gene on chromosome 18 with that of the SSX1/2 genes on the X chromosome. This alteration is present in almost 90 percent of these tumors. Treatment involves resection, followed by chemotherapy and radiation. Given the low prevalence of this tumor, therapeutic recommendations are derived from extremity synovial sarcomas.

## Pleural Epithelioid Hemangioendothelioma

Pleural epithelioid hemangioendothelioma is another rare malignant tumor, which arises from vascular tissue within the pleura. Epithelioid hemangioendothelioma can be found in many other locations in the body such as lung, liver, heart, spleen, and thyroid.[29,30] Pleural epithelioid hemangioendothelioma behaves more aggressively than when encountered in other anatomic locations. Widespread pleural seeding is common. Reactivity with antibodies directed against vimentin, factor VIII, BNH9, and CD31 confirm the diagnosis and a lack of cytokeratin staining helps differentiate this from pleural carcinomatosis. Treatment is relegated to chemotherapy and radiotherapy, which have variable efficacy.

# CONCLUSIONS

Primary pleural tumors are rare but familiarity with diagnosis and treatment is critical for thoracic surgeons. Benign tumors are treated surgically with excellent results. The most common malignant lesion is MPM, which carries a poor prognosis. However, the prospect of long-term survival exists with aggressive multimodality therapy for highly selected patients with early-stage disease, and significant life extension can still be achieved with less extensive therapies for more advanced disease.

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## BENIGN AND MALIGNANT PLEURAL TUMORS BOARD REVIEW QUESTIONS (CHAPTER 21)

1. Which is correct regarding primary pleural tumors?
   A. Solitary fibrous tumors of the pleura are benign lesions.
   B. Malignant transformation of a lipoma is extremely rare.
   C. Malignant mesothelioma occurs at an incidence of 5000 to 10,000 new cases per year.
   D. Synovial sarcomas are small, poorly circumscribed lesions.
   E. Pleural plaques are not associated with asbestos exposure.

2. Which is the most useful imaging modality to further evaluate a pleural abnormality seen on chest x-ray?
   A. Chest ultrasound
   B. CT scan
   C. PET scan
   D. MRI
   E. Thoracoscopy

3. Which of the following would be considered unresectable disease for a patient with malignant mesothelioma?
   A. Involvement of visceral pleura
   B. Involvement of the diaphragm
   C. Involvement of the pericardium
   D. Focus of tumor involving the soft tissue of the chest wall
   E. Invasion of a rib

4. Which of the following interventions, in addition to chemotherapy, would be most appropriate for a patient with malignant mesothelioma involving only the parietal pleura and moderately reduced pulmonary function?
   A. Talc pleurodesis
   B. Pleurectomy and decortication
   C. Chest wall resection
   D. Extrapleural pneumonectomy
   E. No surgery

5. Which of the following interventions, in addition to chemotherapy, would be most appropriate for a patient with bulky malignant mesothelioma that invades the fissures of the lung?
   A. Talc pleurodesis
   B. Pleurectomy and decortication
   C. Chest wall resection
   D. Extrapleural pneumonectomy
   E. No surgery

## ANSWERS

1. **Answer: B.** Malignant transformation of a lipoma is extremely rare. Solitary fibrous tumors can undergo malignant transformation. Malignant mesothelioma occurs at an incidence of 2000 to 3000 new cases per year. Synovial sarcomas are large, well-circumscribed lesions. Pleural plaques are incited by asbestos exposure.
2. **Answer: B.** CT is less expensive and provides high resolution of anatomy. MRI can add detail on vascular or other organ invasion, but is more expensive. Thoracoscopy is used to obtain tissue for diagnosis. Ultrasound and PET are not first-line imaging modalities for an x-ray abnormality.
3. **Answer: E.** Rib invasion is considered a T4 lesion and unresectable. Involvement of the visceral pleura is a T1b lesion. Diaphragm involvement is a T2 lesion. Involvement of the pericardium and focus of tumor involving the soft tissue of the chest wall are both considered T3 lesions.
4. **Answer: B.** For stage I disease, such as tumor involving only the parietal pleura, pleurectomy and decortication is the preferred therapy. Talc pleurodesis offers no chance for cure. Chest wall resection is not indicated, as the tumor does not involve the chest wall. Extrapleural pneumonectomy is reserved for stage II disease. Surgery should be offered to the patient, as moderately reduced pulmonary function is not a contraindication to operation.
5. **Answer: D.** For stage II disease, such as tumor extending into the lung parenchyma, extrapleural pneumonectomy is the preferred therapy. Talc pleurodesis offers no chance for cure. Pleurectomy and decortication is ineffective therapy for a tumor that has extended beyond the pleura. Chest wall resection is not indicated, as the tumor does not involve the chest wall. Surgery should be offered to the patient to obtain maximal survival benefit.

# 22 Diaphragmatic Disorders

*Jarrod D. Predina*
*Sunil Singhal*

## KEY CONCEPTS

- Epidemiology
  - Bochdalek hernias are usually diagnosed in neonates whereas Morgagni hernias tend to be found in adults. Bochdalek diaphragmatic hernias occur in approximately 1:2000 children. Morgagni hernias occur much less frequently than Bochdalek hernias, and account for only 5 percent of all congenital diaphragmatic hernias. Acquired sliding (type I) hiatal hernias may be found in up to 15 percent of the population, and account for 95 percent of acquired diaphragmatic defects. The remaining 5 percent of acquired diaphragmatic hernias are composed primarily of paraesophageal (type II) hernias. Acquired diaphragmatic hernias are often diagnosed in patients with risk factors for increased intra-abdominal pressures. Diaphragmatic paralysis most commonly occurs following cardiac surgery procedures, with incidences ranging from less than 1 percent to approximately 10 percent. Most diaphragmatic tumors are metastatic in nature, and primary tumors of the diaphragm are quite rare.
- Pathophysiology
  - In neonates, Bochdalek hernias result in abdominal viscera assuming an intrathoracic position, typically into the left hemithorax. This displacement often impairs growth of the ipsilateral lung, causes mediastinal deviation to the contralateral chest, pulmonary compromise, and pulmonary hypertension. Morgagni hernias also result in abdominal viscera herniation into the chest; however, presenting symptoms more often are related to bowel obstruction. Sliding hiatal (type I) hernias are defined as a supradiaphragmatic displacement of the gastroesophageal (GE) junction. The abnormal anatomy impairs lower esophageal sphincter (LES) function and results in reflux symptoms. Paraesophageal (type II) hernias occur when the gastric fundus assumes a supradiaphragmatic position, whereas the GE junctions remain in its normal anatomical location. Diaphragmatic paralysis may result from any abnormality along the neuromuscular axis. Diaphragmatic tumors are most commonly the result of metastatic tumors originating in surrounding organs.
- Clinical features
  - In extreme circumstances, Bochdalek hernia may result in early respiratory compromise requiring prompt surgical interventions or extracorporeal membrane oxygenation (ECMO). Those diagnosed with Morgagni hernia often present with abdominal symptoms and discomfort. The abnormal anatomy associated with sliding (type I) hiatal hernias impair LES function, thus producing reflux symptoms such as "heartburn" and abdominal discomfort. Reflux may predispose patients to develop esophagitis and esophageal cancer. Gastric strangulation is the primary concern for those diagnosed with paraesophageal (type II) hiatal hernias. Both unilateral and bilateral diaphragmatic paralysis may be observed and, in a well-compensated patient, are compatible with normal activity. Diaphragmatic tumors are normally asymptomatic and found incidentally.
- Diagnostics
  - Plain chest radiograph is diagnostic for diaphragmatic hernias, whereas computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound may play adjunctive roles. Congenital defects may be found on prenatal ultrasound. Contrast studies may also reveal important anatomy of acquired hiatal hernias. Diaphragmatic paralysis can be suggested by plain chest radiography as indicated by elevated diaphragmatic boarders. Fluoroscopic evaluation ("sniff test") may also aid in the diagnosis of diaphragmatic paralysis. Recently, ultrasound evaluation of the diaphragm has become more common. Diaphragmatic tumors may be incidentally found with a number of modalities, and should be further evaluated using CT and MRI techniques.
- Treatment
  - Operative repair for Bochdalek and Morgagni hernias require reducing herniated abdominal contents,

resecting the hernia sac, and closing the diaphragmatic defect primarily or with a synthetic patch. Sliding (type I) hiatal hernias should first be addressed with medical management. Surgery is indicated for patients with recalcitrant symptoms, reflux complications, and signs of high-grade dysplasia in Barrett's esophagus. Surgery aims to restore the GE junction to the abdomen and uses fundoplication to minimize reflux. Paraesophageal (type II) hiatal hernia requires surgical reduction of the proximal stomach, resection of the hernia sac, and diaphragmatic defect closure. Diaphragmatic paralysis is often transient, requiring no intervention. In the case of treatment, diaphragmatic placation may be required. Surgical resection of all diaphragmatic tumors is advocated and should include en bloc resection of surrounding pleural and peritoneal layers followed by defect closure.

- Outcomes/prognosis
  - Repair of congenital diaphragmatic hernia is safe and usually successful. The morbidity and mortality associated with Bochdalek hernia are due to inadequate pulmonary development and pulmonary hypertension. Prompt repair in neonates with careful cardiopulmonary management has dramatically improved outcomes of the last 15 years. Surgical correction of acquired hiatal hernias is also associated with marked improvements and excellent long-term prognosis. Diaphragmatic paralysis usually resolves spontaneously within 1 year of injury. In the case of persistent paralysis, diaphragmatic plication is a well-tolerated procedure that produces both clinical and functional improvements. Surgical resection of benign diaphragmatic lesions is well tolerated; however, malignant lesions are associated with poor outcomes as recurrent disease is common.

## INTRODUCTION

The term "diaphragm" originates from the Greek words dia (in between) and phragma (fence). This reflects the diaphragm's anatomical role in separating the torso into the thoracic and abdominal cavities. Functionally, the diaphragm is the principal muscle of respiration.

To review, embryologic development of the diaphragm is a process that occurs between the fourth and eighth week of gestation.[1] The organ is formed by the fusion of tissues from four different sources. First, the septum transversum, a mass of mesodermal tissue located between the primitive heart tube and liver, gives rise to the central tendon of the diaphragm. This process produces two spaces (pleuroperitoneal canals) for the development of the lungs. As the lungs develop, they form bilateral folds, which fuse with the septum transversum to form bilateral pleuroperitoneal membranes.[1] Myoblasts penetrate the pleuroperitoneal membranes to form the muscular part of the diaphragm. Also, the dorsal mesentery of the esophagus becomes invaded by myoblasts and ultimately forms the crura of the adult diaphragm. Finally, the body wall contributes portions to the peripheral diaphragm. During the fourth week of fetal development, the primitive diaphragm becomes innervated by the phrenic nerves (C3, C4, and C5). By week 8, the diaphragm descends as a result of displacement by the rapidly growing neural tube. A delay or alteration in the embryologic structuring can result in a diaphragmatic hernia or congenital eventration.

Anatomically, the diaphragm is skeletal muscle composed of two distinct parts—the costal and crural aspects.[1] The costal muscle, located peripherally, is thin and causes downward displacement of the diaphragm. The costal part of the diaphragm allows the diaphragm to flatten and the lower ribs to lift, resulting in inspiration. The crural aspect of the diaphragm is thicker, supports the heart, and plays a lesser role in respiration. Both groups are innervated by the phrenic nerve. The pericardiacophrenic artery, musculophrenic artery, and superior phrenic arteries extend to the superior side of the diaphragm while the caudal area is supplied by the inferior phrenic arteries. The inferior phrenic arteries branch off the aortal hiatus directly from the aorta or from the celiac trunk. Direct branches of the aorta also vascularize the dorsal part of the diaphragm.

In the adult, the diaphragm is the primary muscle of inspiration and is responsible for 75 to 80 percent of the air brought into the lungs during quiet breathing.[2] During light inspiration, the 2 domes of the diaphragm flatten to some extent, whereas the central tendon remains almost stationary. The diaphragm typically descends 1 to 2 cm during quiet breathing but may lower as much as 6 to 7 cm with forced inspiration. The peripheral parts of the diaphragm unwrap from the lateral walls of the chest by contraction during deep breathing. Both movements widen the costodiaphragmatic recesses, which the lungs subsequently expand to partially fill.

## DIAPHRAGMATIC HERNIAS

There are four hernias we will consider (Fig. 22-1): two congenital hernias (Bochdalek and Morgagni) and two acquired defects (sliding and paraesophageal).

### Congenital Diaphragmatic Hernias

#### BOCHDALEK (POSTEROLATERAL) HERNIA

Despite major advances in prenatal diagnosis and management, infants with Bochdalek diaphragmatic hernias diagnosed at birth (1/4000 live births) have a poor prognosis.[3] Bochdalek hernia is a posterolateral hiatal defect in the diaphragm caused by a failure of the pleuroperitoneal canal fusion during fetal development. More than 80 percent occur

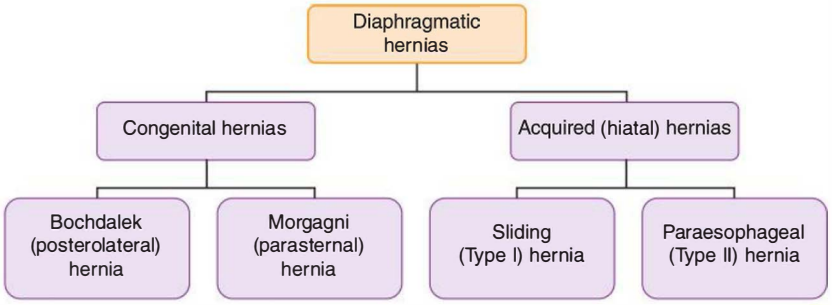



**FIGURE 22-1** Classification of diaphragmatic hernias.

in the left hemithorax, and typically are through a small circular defect (Fig. 22-2). Only 10 percent have a true hernia sac. When the intestines return to the abdomen from the yolk sac at 10 weeks gestation, the abdominal organs may herniate into the thorax through this defect. The pressure of abdominal viscera in the thoracic cavity results in a decrease in the number of bronchial branches, total number of acini, and number of vessels. Typically this results in impaired growth of the ipsilateral lung. However, in extreme cases, when the mediastinum is forced to the contralateral

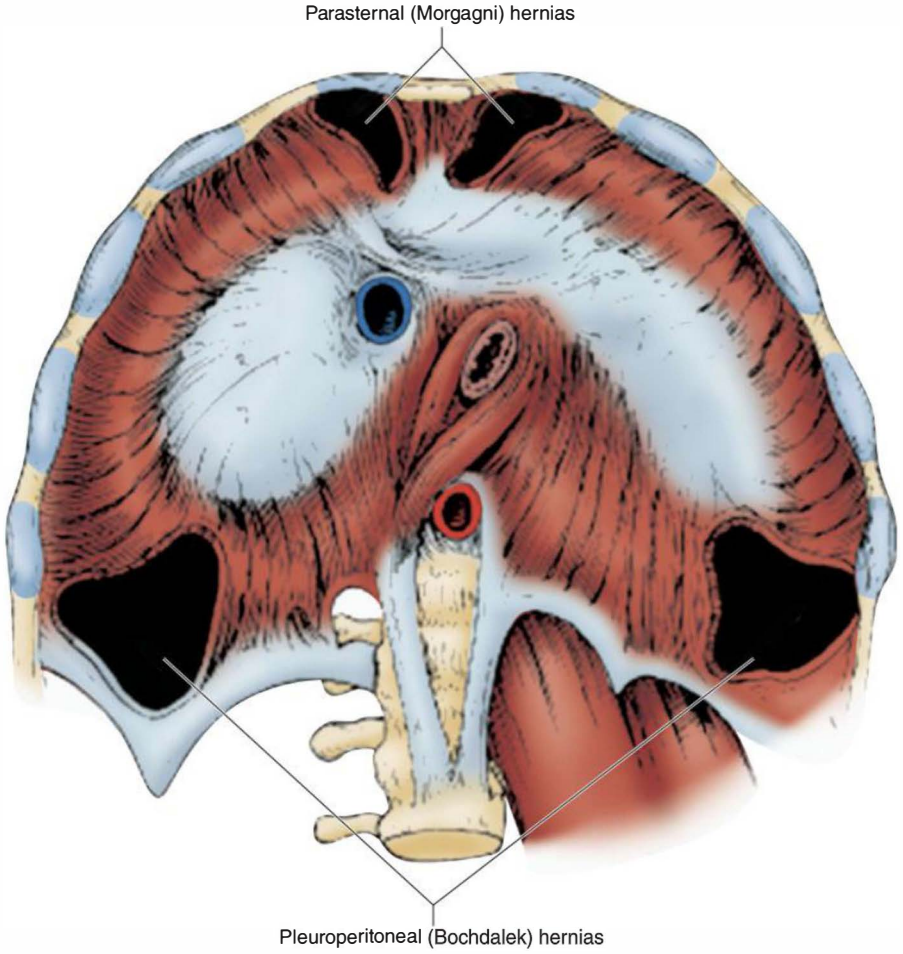



**FIGURE 22-2** Pictorial representation describing location of common congenital diaphragmatic hernias (Bochdalek and Morgagni). (Reproduced with permission from Doherty GM (ed.) *Current Diagnosis & Treatment: Surgery*, 13th ed. McGraw-Hill, Inc, 2010. Fig. 20-17.)

side of the chest, the contralateral lung may also be affected. Herniation of the viscera through the defect usually occurs during the pseudoglandular stage of lung development.

They are commonly associated with additional anomalies including congenital heart defects, hydronephrosis, renal agenesis, intestinal atresia, extralobular sequestration, hydrocephalus, anencephaly, and spina bifida.

Bochdalek hernias may result in life-threatening respiratory compromise as early as the first hours or days of life.[3] The timing of presentation is dependent on the degree of pulmonary hypoplasia, which is the main cause of morbidity and mortality associated with this disorder. Occasionally, the defect may result in respiratory distress or feeding intolerance in later infancy or childhood or may be identified on a radiograph obtained for unrelated reasons. The other element that contributes to the pathophysiology of this disease is pulmonary hypertension—this condition mimics normal fetal circulation and is termed persistent fetal circulation. This condition may result in hypoxemia and acidosis (Fig. 22-3). Severe pulmonary hypertension forces right-to-left shunting through the persistent foramen ovale and the patent ductus arteriosus.

Almost 50 percent of these congenital diaphragmatic hernias are identified during prenatal ultrasound examination.[4] The diagnosis can later be confirmed by a chest radiograph that characteristically demonstrates abdominal contents in the chest with mediastinal deviation away from the affected side (Fig. 22-4). The differential diagnosis includes congenital cystic adenomatoid malformation, other cystic diseases of the lung, and eventration of the diaphragm. Visualization of the naso- or oralgastric tube above the diaphragm also supports the diagnosis. The prenatal diagnosis of right-sided defects is extremely difficult because of the similar echogenicity of the liver and lung.

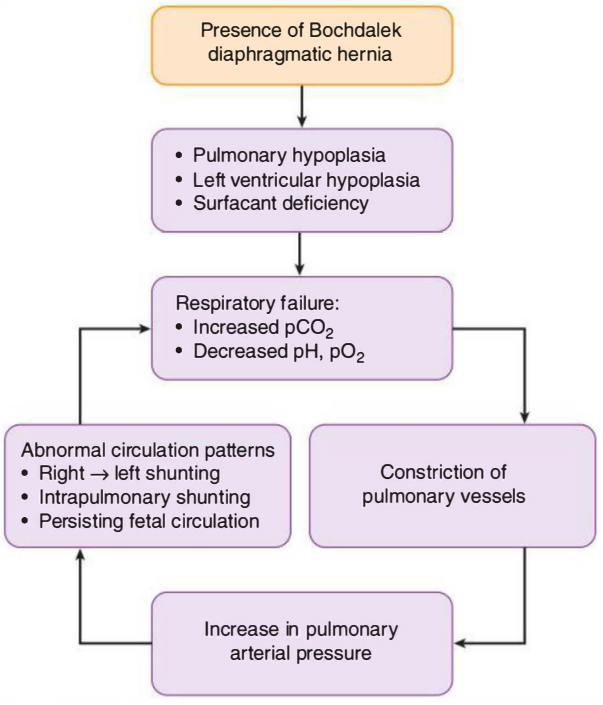



**FIGURE 22-3** Flow-diagram describing pathophysiology of acute respiratory failure associated with congenital diaphragmatic hernia in neonates. (Adapted from Ashcraft KW (ed.) *Pediatric Surgery*, 3rd ed. Philadelphia: WB Saunders, 2000:302.)

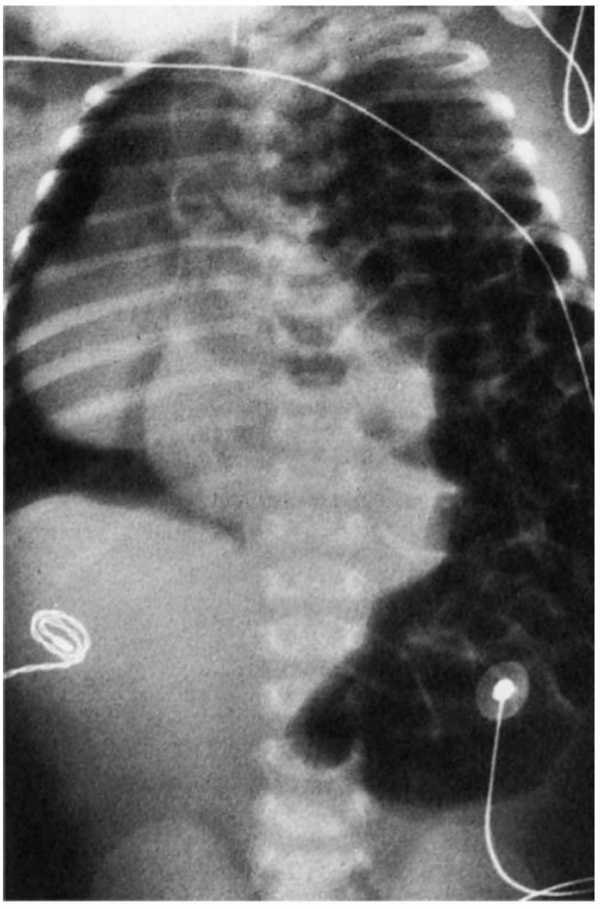


**FIGURE 22-4** Chest x-ray of a neonate with a Bochdalek hernia. Chest radiograph demonstrate abdominal organs within the left hemithorax and mediastinal shift to the right. (Reproduced with permission from Kaplan JA, Slinger PD. *Thoracic Anesthesia*, 3rd ed. Philadelphia: Churchill Livingstone, 2003:355. Copyright Elsevier.)

If a patient presents with respiratory distress at birth, the child should be promptly intubated and nasogastric decompression initiated to minimize visceral distention. Mechanical ventilation with 100 percent $F_iO_2$ and low airway pressures (<25 mm Hg and 5 of positive end-expiratory pressure (PEEP)) should be used. The patient should then be transported to a facility capable of extracorporeal membrane oxygenation (ECMO). Indication to place a baby on ECMO includes an alveolar–arterial oxygen gradient greater than 600 for 8 h, oxygen index greater than 40, pH <7.15, $P_aO_2$ <55, and progressive barotrauma. ECMO is contraindicated if the patient has preexisting weights less than 2 kg,

intraventricular hemorrhage, or has other abnormalities incompatible with life.

Repair of a Bocadaleck hernia has previously been considered a surgical emergency; however, the scheme of emergency operative repair immediately after birth has resulted in mortality rates greater than 50 percent. Recent trends include alternative forms of management, such as delayed operation, ECMO, inhaled nitric oxide, and partial liquid ventilation, all with improved results. Recent studies have demonstrated preoperative stabilization results in improvement of pulmonary compliance prior to repair.[4] Once stable, the repair can be performed through a paramedian incision or subcostal incision. A transthoracic approach has also been advocated by some for right-sided hernias. From the abdominal approach, the viscera can be returned from the chest and the hernia sac may need to be excised if present. The lung tissue should be examined; however, attempts to expand the hypoplastic lung should be avoided. Extralobar pulmonary sequestrations are resected at the time of hernia repair.

A small diaphragmatic defect is closed with permanent suture and Teflon pledgets. Larger defects, or defects whose edges may be under tension, can be closed with synthetic sheet material. Typically, bilateral chest tubes are left in place and connected to water-seal. Intra-abdominal anomalies may be corrected at the time of hernia repair if the patient's condition is stable, although there remain center-to-center preferences regarding this step. In some cases, abdominal wall fascia may not be closed primarily and these circumstances should be managed as large abdominal wall defects.

Postoperative management should aim to reduce pulmonary vascular resistance, improve oxygenation, and treat persistent fetal circulation. Frequent arterial blood gas determinations coupled with continuous pulse oximetry or transcutaneous partial pressure of oxygen and carbon dioxide monitoring provide a reliable mechanism of ventilatory status. A variety of vasodilators have been used to prevent and reverse pulmonary hypertension. It is important to realize that minor changes in ventilation can precipitate intense pulmonary vasoconstriction. Finally, one should consider that the lungs are at risk of barotrauma. As a last resort, ECMO may need to be initiated to reverse pulmonary hypertension if conventional methods fail.

In the absence of additional lethal anomalies, mortality is directly related to the degree of pulmonary hypoplasia. Other prognostic indications associated with poor outcome include additional anomalies, polyhydramnios, presence of an intrathoracic stomach bubble, and underdevelopment of the left heart region. Although the majority of these patients present within the first few days of life, patients may present later in life. This cohort of patients often presents with a variety of respiratory symptoms or sometimes bowel obstruction.

### MORGAGNI (RETROSTERNAL) HERNIA

Morgagni hernia was initially described by Morgagni in 1769. Morgagni hernias are rare and account for less than 5 percent of all diaphragmatic hernias. Unlike Bochdalek hernias, patients with Morgagni hernias typically present later in life.[3] Morgagni hernias are hypothesized to arise from the incomplete fusion of the transverse septum to fuse with the sternum and resulting abnormalities of the foramen of Morgagni (Fig. 22-2). These hernias typically are true hernias and possess a hernia sac. Commonly, the defect contains a piece of omentum that enlarges as the person grows and produces the mass within the hernia sac. However, colon and small intestine are capable of passing through larger defects. A right-sided defect occurs in 90 percent of the cases because the left side is protected by the pericardium.

Small Morgagni hernias typically remain unrecognized and asymptomatic in young children, and are diagnosed in adults. Larger ones, however, can produce severe respiratory symptoms in children. Women tend to be more commonly affected than men. Surprisingly, dyspnea is only occasionally observed in patients' past early childhood. Plain chest radiographs demonstrate a density, either solid or containing air, adjacent to the right or left side of the heart. A CT or contrast study is occasionally indicated to confirm the diagnosis. A contrast study can identify whether the stomach, small bowel, or colon is above the diaphragm in the parasternal position.

An abdominal approach for surgical repair is preferred for this hernia, and a subcostal or right epigastric paramedian incision is advocated. At the time of surgery, the contents of the hernia should be reduced into the peritoneal cavity by gentle retraction and the margins of the hernia sac should be identified. When possible, the sac should also be excised. The repair of small muscular defects is made with interrupted mattress sutures. Larger defects should be repaired using synthetic patch material. Occasionally, it may be necessary to manipulate the diaphragm to the posterior aspects of the sternum and to the posterior rectus sheath for full closure of the defect.

## Acquired Hiatal Hernias

Acquired hiatal hernias are classified according to their anatomic characteristics. Sliding hernias (type I) are characterized by a dome-shaped upward migration of the gastroesophageal (GE) junction into the posterior mediastinum. Paraesophageal hernias (type II) are characterized by an upward dislocation of the gastric fundus alongside a normally positioned GE junction. Sliding hernias are much more common than paraesophageal hernias.

### SLIDING (TYPE I) HIATAL HERNIA

Most sliding hernias are acquired defects. In this type of hernia, the GE junction moves through the esophageal hiatus into the visceral mediastinum (Fig. 22-5). The esophageal hiatus is formed by muscle fibers of the right crus of the diaphragm with little or no contribution from the left crus. These fibers overlap inferiorly where they attach over and along the right side of the median arcuate ligament. Sliding hernia occurs as a result of a weakening or attenuation of

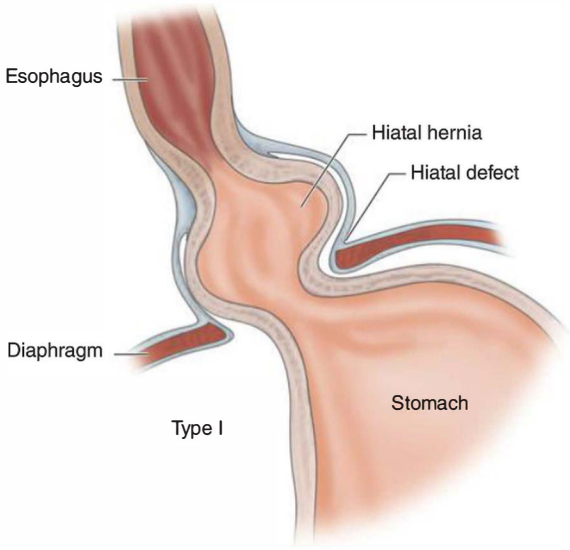



**FIGURE 22-5** Schematic demonstrating anatomy of sliding (type I) hiatal hernia. (Reproduced with permission from Sugarbaker DJ, Bueno R, Krasna MJ, Mentzer SJ, Zellos L (eds.) *Adult Chest Surgery*. McGraw-Hill, Inc, 2009. Fig. 29-3.)

the phrenoesophageal ligament. Enlargement of the hiatus occurs by separation of the crura, posteriorly and laterally, in proportion to the amount of stomach protruding through it. Early in the process, the GE junction may be located below the diaphragm, but with straining, coughing, or recumbency may transiently migrate above it. As the hernia enlarges, this "sliding" component no longer occurs and a GE junction assumes a permanent supradiaphragmatic position.

Over time the intrinsic sphincteric component of the diaphragm diminishes. The presence of the sliding hiatal hernia is in itself of little consequence and is a common finding that occurs in over 10 to 15 percent of the population.[5] Morbidity associated with sliding hernias is dependent on the reflux of gastric contents into the lower third of the esophagus (Fig. 22-6). Whether or not esophagitis develops is determined by multiple factors and, even with significant reflux, symptoms may not be apparent. As the reflux process continues, loss of surface epithelium in the esophagus leads to superficial ulcerations. These ulcerations can cause scarring during periods of healing and contracture may lead to strictures (Fig. 22-6).

Sliding hernias are caused by multiple factors that result in increased intra-abdominal pressure: pregnancy, obesity, vomiting, and vigorous esophageal contractions. Typical presenting symptoms often include retrosternal or epigastric heartburn, postural regurgitation (especially when lying on the right side), and intermittent dysphagia. These symptoms are generally secondary to (1) reflux of gastric contents due to incompetence of the lower esophageal sphincter (LES) and (2) varying degrees of esophagitis. Symptoms are typically worse after meals and aggravated by position such as

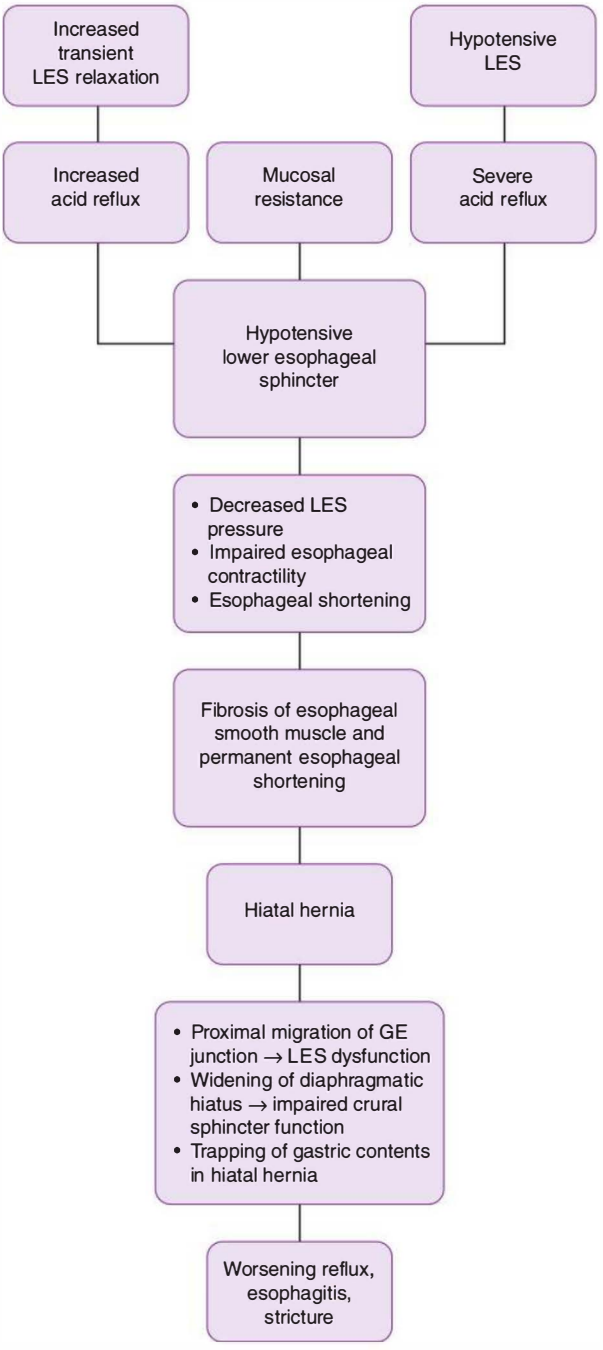
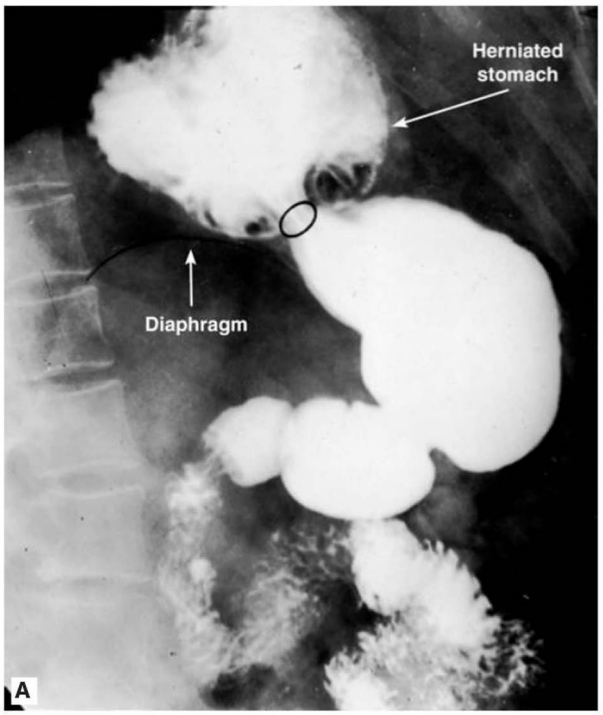
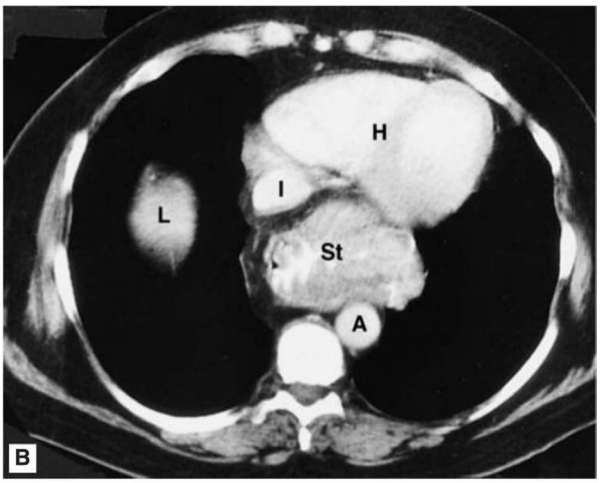



**FIGURE 22-6** Schematic describing mechanism of gastroesophageal reflux disease (GERD). Increased transient lower esophageal sphincter (LES) relaxation is the predominant mechanism of GERD. A subset of patients with GERD have hypotensive LES and usually have severe reflux disease. (Redrawn from Buttar NS, Falk GW. Pathogenesis of gastroesophageal reflux and Barrett esophagus. *Mayo Clin Proc* 2001; 76:226–234.)



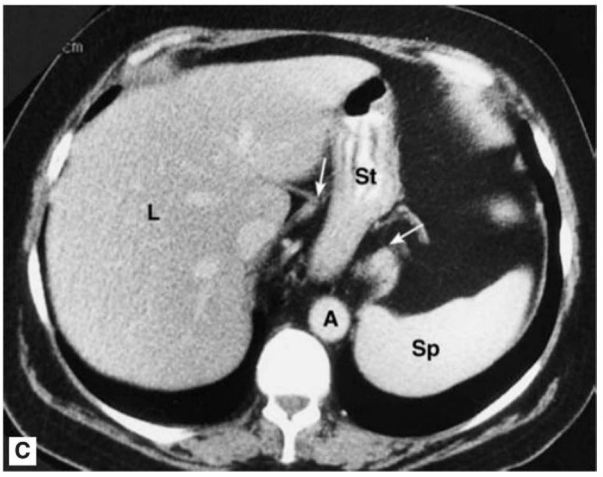




**FIGURE 22-7** Hiatal hernia. **A.** Upper GI demonstrating sliding hiatal hernia. (Reproduced with permission from Doherty GM (ed.) *Current Diagnosis & Treatment: Surgery*, 13th ed. McGraw-Hill, Inc, 2010. Fig. 20-10.) **B.** CT scan through the lower chest revealing herniation of the proximal stomach (St) through the esophageal hiatus into the inferior mediastinum. **C.** Image obtained several centimeters inferior demonstrates widening of the esophageal hiatus (arrows) and proximal stomach herniation. A, aorta; H, heart; I, inferior vena cava; L, liver; Sp, spleen. (Reproduced with permission from Pearson FG, Cooper JD, Deslauriers J, et al., (ed.) *Thoracic Surgery*, 2nd ed. New York: Churchill Livingstone, 2002:1520. Copyright Elsevier.)

lying down, stooping, bending over, or straining. Relief may come with sitting or standing.

The diagnosis of a hiatal hernia can be made using chest radiography, which may suggest a lower posterial mediastinal, retrocardiac mass, often with an air–fluid level. Barium esophagogram may confirm the diagnosis (Fig. 22-7A), but is seldom required. CT scan is often required to confirm the presence of a hiatal hernia (Figs. 22-7B and 22-7C).

Medical treatment is advocated for patients with mild or transient symptoms in whom esophagitis is absent or mild. The goal of medical treatment is to minimize reflux and the irritative effects of gastric secretions. An ideal regimen entails behavior modification and medication. A patient should attempt to ingest smaller meals and avoid going to bed within 3 h of a large meal. Alcohol, caffeine, and chocolate should be eliminated from the diet. A patient should also avoid tight fitting clothing, lose weight, and elevate the head of the bed. Pharmacologically, antacids can be prescribed for before meals and bedtime to minimize the acidity of fluid in the esophagus. $H_2$-receptor antagonists and proton-pump inhibitors (PPIs) can minimize acid secretions in the stomach. The introduction of PPIs has significantly advanced the medical management of gastroesophageal reflux disease (GERD). These drugs block the $H^+$-$K^+$-adenosine triphosphate (ATPase) pump. PPIs can decrease acid secretion by 75 to 90 percent of basal and postprandial status. In the absence of symptoms, no treatment is indicated for an uncomplicated sliding esophageal hernia.

Esophagoscopy should also be carried out on all patients with symptoms of GE reflux to assess esophagitis and intestinal metaplasia. Esophagoscopy also allows for assessment of pliability of the esophageal wall, location esophagogastric junction with relation to the diaphragm, and the presence of a comorbid paraesophageal hernia. A biopsy of the mucosa should be obtained to evaluate for Barrett's esophagus. Esophagogastroscopy should be used to rule out specialized intestinal columnar epithelium within 3 cm of the GE junction.

Indications for surgery include scenarios when severe symptoms persist despite optimal nonoperative management.[6] Patients who also develop complications from reflux esophagitis such as recurrent aspiration pneumonitis or peptic strictures are also candidates.[6] Signs of high-grade dysplasia in Barrett's esophagus should warrant repair of the hernia as ongoing damage of the distal esophagus due to GERD and development of Barrett's esophagus can have serious consequences. The mere presence of a sliding hiatal hernia is *not* an indication for an operation.

Surgical goals are twofold: prevent reflux and treat the esophagitis. The ultimate goal of the surgical intervention is to reproduce the valve-like mechanism of the distal esophagus by wrapping the fundus of the stomach and the GE junction.[6] The wrap must not interfere with passage of food into the stomach; however, it must prevent reflux of gastric contents into the esophagus. The most commonly employed procedure is the Nissen fundoplication, which in short is a 360-degree wrap performed via either laparotomy or laparoscopy.

The operation of choice depends on the individual needs of the patient and expertise of the surgeon. Factors that influence the choice include whether a thoracic or abdominal approach is advantageous, whether the patient has already had a previous antireflux repair, whether a resection or esophagomyotomy is necessary, and patient's body habitus. The principle of these procedures (Nissen, Belsey, Dor Toupe) is the same. The surgeon restores the GE junction to the abdomen and reduces the hiatal hernia while also approximating the diaphragmatic crurae by wrapping the gastric fundus around the distal esophagus (fundoplication). Restoration of the distal esophagus to the positive-pressure environment of the abdomen also plays a role in preventing reflux. These procedures may require a lengthening procedure of the esophagus ("Collis procedure").

As previously mentioned, antireflux procedures for sliding hiatal hernias can be performed a number of ways. Laparoscopic Nissen fundoplication and open laparotomy accomplish the same operation, although the laparoscopic approach has less perioperative discomfort. Long-term outcome is the ultimate motivation and depends on the success of the primary operation; therefore, the patient should obtain best operation at the disposal of the surgeon.

## PARAESOPHAGEAL (TYPE II) HIATAL HERNIA

Paraesophageal hiatal hernias are much less common than sliding hernias. The hernia is a result of focal phrenoesophageal membrane weakening, typically located anteriorly and laterally to the esophagus (Fig. 22-8). The gastric cardia and lower esophagus remain below the diaphragm in the normal anatomic location; however, gastric fundus and abdominal viscera protrude through the defect into the mediastinum. The protruding organs are circumferentially covered by a layer of peritoneum that forms a true hernia sac, unlike the sliding hernia in which the stomach forms the posterior wall of the hernia sac. As the superior stomach ascends into the chest, obstruction can result at the diaphragm.

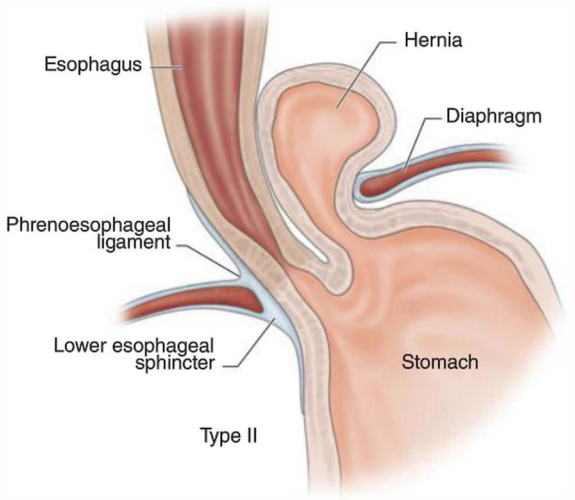



**FIGURE 22-8** Schematic demonstrating anatomy of paraesophageal (type II) hiatal hernia. (Reproduced with permission from Sugarbaker DJ, Bueno R, Krasna MJ, Mentzer SJ, Zellos L (eds.) *Adult Chest Surgery*. McGraw-Hill, Inc, 2009. Fig. 29-3.)

Patients most commonly describe postprandial retrosternal fullness, which may be relieved by regurgitation or belching. Reflux symptoms may or may not be present, and dysphagia is rare. Possible complications include bleeding, incarceration, volvulus, obstruction, strangulation, and perforation. Gastritis and ulceration have been visualized in as many as one-third of patients with paraesophageal hernias. It is suspected that these ulcerations are the result of inadequate gastric emptying and torsion of the gastric wall, particularly after repeat incarcerations, which subsequently impair the blood supply. Chronic bleeding from gastritis or ulceration leads to iron deficiency anemia with resultant fatigue and exertional dyspnea. Respiratory complications may be associated with a paraesophageal hernia and consist of dyspnea from mechanical compression and recurrent pneumonia from aspiration. In the event of gastric volvulous or obstruction, patients may describe severe nausea, abdominal pain, and an inability to regurgitate.

The diagnosis of paraesophageal hiatal hernia is typically first suspected because of an abnormal radiograph of the chest. The most common finding is a retrocardiac air bubble with or without an air-fluid level. The hernia sac and its contents occasionally protrude into the right thoracic cavity. A barium study of the upper gastrointestinal tract is the diagnostic study of choice. Once the diagnosis is established, the functional effect on the competence of the LES should be determined by endoscopy or esophageal function testing.

There is no medical treatment regimen for patients with paraesophageal hiatal hernia. Because of the potentially serious and life-threatening complications associated with this disorder (namely, specifically gastric strangulation), the mere presence of the defect has been considered an indication for

operation.[7] When a patient presents with gastric volvulus and obstruction, decompression with a nasogastric tube must be promptly performed. When unable to decompress a gastric volvulus, patients should undergo immediate operative intervention, whether or not signs of toxicity exist.

The surgical approach for paraesophageal hernia remains controversial. A thoracic approach allows for superior hernia dissection, whereas an abdominal approach is technically less demanding and allows for simultaneous placement of a gastrostomy tube. When the patient has overt signs of significant reflux esophagitis preoperatively, an antireflux procedure should be performed, thus securing the stomach within the peritoneal cavity and repairing the crural defect. In these scenarios, the procedure may be accomplished using laparoscopic techniques. Completion of a concomitant fundoplication has no proven role.

## PARALYSIS OF THE DIAPHRAGM

Paralysis of the diaphragm may be a manifestation of abnormalities located at any point along the neuromuscular axis (Fig. 22-9). In adults, however, the most common cause of hemidiaphragm paralysis is iatrogenic phrenic nerve injury, particularly from cardiac operations where topical cold solutions are used. Internal mammary artery takedown is also associated with phrenic nerve injury. The left nerve is more frequently involved. With new trends of limited opening of the pleural space, phrenic nerve injury has become a less common problem. Other techniques to minimize this injury include lung inflation to protect the nerve from contact with ice slush. Furthermore, when injury does occur, it is usually temporary and fully resolves within 6 to 12 months. Other less common etiologies of phrenic nerve paralysis include trauma, mediastinal surgery infection, neoplasm, neuromuscular disease, and lead poisoning. Occasionally, idiopathic diaphragmatic paralysis is also seen in adults but is thought to be caused by subclinical viral infections. Again, these usually manifest unilateral paralysis, though bilateral injury has been reported.

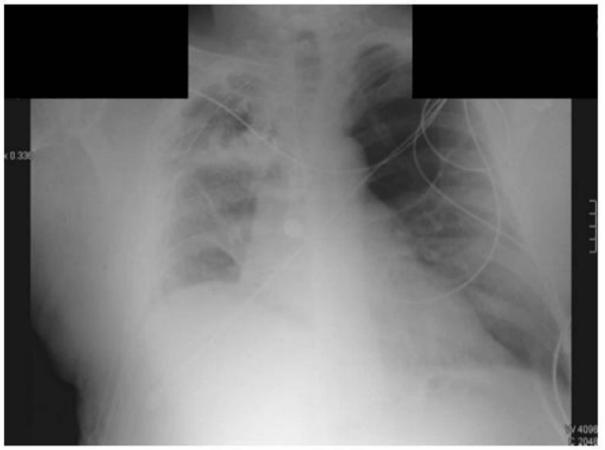


**FIGURE 22-9** Postoperative PA chest radiography demonstrating an elevated right hemidiaphragm. The etiology of this finding was a right paramediastinal mass, involving the phrenic nerve, which required surgical resection. (Image courtesy of Vincent Lotano, MD at the University of Pennsylvania Health System.)

Like adults, the most common cause of unilateral diaphragmatic paralysis in children is injury to one of the phrenic nerves during a cardiac surgery procedure. Redo operations have almost twice the incidence of phrenic nerve injury. Birth trauma and removal of a mediastinal tumor are occasional causes of nerve injury in children.

Previous reports have suggested that a reduction of 20 to 30 percent in the vital capacity and the total lung capacity can be observed with isolated hemidiaphragm paralysis. Perfusion is also diminished, however, typically to a lesser extent. Despite these findings, adults with unilateral diaphragm paralysis typically survive without significant respiratory compromise. Bilateral diaphragmatic paralysis is also often compatible with life in adults; however, it is associated with excessive compensatory movement of the accessory muscles of respiration. In infants and young adults, however, these diagnoses can be life threatening.

Pulmonary function tests often reveal decreased vital capacity in the erect position, which may be further decreased by 50 percent while supine. Lung compliance is also reduced, likely as a result of widespread atelectasis that can be visualized on chest roentogram. On inspiration, the intercostal-accessory muscles contract by expanding the rib cage and producing negative pleural pressure that draws the diaphragm and the abdominal viscera upward into the thoracic cavity. In the case of unilateral paralysis, the affected hemidiaphragm paradoxically moves upward on inspiration as a result of generated negative intrathoracic pressure. When both hemidiaphragm are paralyzed, both will move upward on inspiration.

Paralysis of the diaphragm can be suggested by basilar atelectasis on a plain chest radiograph. Ultrasound studies showing paradoxic diaphragmatic motion with a sniff test have largely replaced fluoroscopy as the gold standard. Unilateral diaphragmatic paralysis can be distinguished by the upward movement of the hemidiaphragm with sniffing. The paradoxical movements may not be observed with normal, deep inspiration as the contralateral diaphragm stretches the thoracic cavity causing a slight descent paralyzed diaphragm. Percutaneous electrical stimulation of a suspected phrenic nerve can also yield information regarding the nerve and the diaphragm function.

Conservative therapy is the treatment of choice for adults, as symptoms are often transient and phrenic nerve regeneration capacity. In the case of a completely severed nerve, direct nerve repair is rarely successful. Diaphragmatic plication works well for the patient with prolonged, severe symptoms, but should only be implemented after 1 year of the initial diagnosis (to allow for adequate time for phrenic nerve regeneration). In infants, mechanical ventilation should be the initial treatment of choice. These children are

typically placed with the involved side down and treated with continuous positive airway pressure. If resolution does not occur within 2 weeks, operative intervention is undertaken by plication of the paralyzed diaphragm. Interestingly, plication does not preclude the return of diaphragmatic function.

The objective of diaphragm placation is to reduce the muscle into a more natural (flat) position and to minimize paradoxical motion and associated shifts of the mediastinum on inspiration. Ultimately, this will allow for more efficient ventilation mechanics as the contralateral diaphragm and other accessory muscles are used. We tend to use a thoracic approach, although both open and laparoscopic approaches may be used. The lateral and posterior aspects of the diaphragm are plicated with pledgeted sutures and in a horizontal mattress pattern. These stitches should be placed approximately 1.0 cm apart, and careful consideration should be given to avoid incorporating branches of the phrenic nerve. The goal should be to ultimately make the diaphragm moderately taught. Another approach involves resection of muscle followed by primary closure.

## DIAPHRAGMATIC TUMORS

Primary tumors of the diaphragm are uncommon. Most are mesothelial in origin, although neurogenic tumors do occur. The majority of diaphragmatic tumors are discovered in the fifth to seventh decade of life, with most being benign. Simple cysts have been most commonly found, although lipomas, fibromas, and benign neurogenic tumors are possibilities. Malignant primary lesions are far less common than benign lesions, and are most frequently sarcomas of muscle or connective tissue origin.[8] Tumors are typically asymptomatic and usually noted on routine radiographs of the chest or found incidentally at time of surgery. Symptoms, when present, include lower chest pain, cough, dyspnea, and abdominal fullness. More commonly than primary diaphragmatic tumor, the diaphragm is invaded secondarily by malignant neoplasms originating from surrounding structures. The diaphragm may also be a site of distant metastasis.

Computed axial tomography and magnetic resonance imaging are usually necessary for full visualization of diaphragmatic tumors. Angiography may serve a supplemental role when liver involvement is likely. The differential for a suspected diaphragmatic mass includes an infectious collection (including *mycobacterium tuberculosis*), hematoma, congenital abnormality, and hernia. On CT scans, lipomas typically appear large, sharp-bordered, and smooth.

Resection and reconstruction of the diaphragm usually does not represent a technical challenge, and is indicated for all tumors of the diaphragm.[8] During tumor resection, the pleural and peritoneal layers should be excised en bloc with the diaphragm. The remaining defect is either closed primarily using nonabsorbable mattress sutures or with a prosthetic soft tissue patch of GORE-TEX or polypropylene mesh. There is minimal morbidity and mortality from diaphragmatic resections, and fulminant respiratory compromise is quite rare. The overall prognosis is quite good for benign lesions. Unfortunately, for malignant tumors, recurrence is common and patients tend to have poor long-term outcomes.

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## DIAPHRAGMATIC DISORDERS BOARD REVIEW QUESTIONS (CHAPTER 22)

1. Which is correct regarding congenital diaphragmatic hernias?
   A. These hernias are not commonly associated with other congenital anomalies.
   B. A neonate with a Bochdalek hernia and a pH <7.25 should be placed on ECMO.
   C. A Morgagni hernia usually presents with respiratory compromise.
   D. Most congenital diaphragmatic hernias can now be diagnosed on prenatal ultrasound.
   E. Mortality is unrelated to pulmonary hypoplasia.

2. Which is correct regarding diaphragmatic paralysis?
   A. It is often associated with significant morbidity
   B. Is most commonly idiopathic
   C. Usually requires either diaphragmatic plication or pacing
   D. Is frequently bilateral
   E. Symptoms usually resolve within a year

3. Which of the following is *not* an indication for surgical intervention in a patient with a type I hiatal hernia?
   A. Recalcitrant severe symptoms despite maximal medical therapy
   B. Development of an esophageal stricture
   C. Migration of more that 50% of the stomach into the chest
   D. Recurrent aspiration pneumonitis
   E. High-grade dysplasia in the distal esophagus

4. Which of the following is correct regarding diaphragmatic tumors?
   A. They usually originate from the diaphragmatic muscle.
   B. The majority are discovered in the fifth to seventh decade of life.
   C. Most primary diaphragmatic tumors are malignant.
   D. Surgical resection of malignant tumors offers the best chance at favorable outcomes.
   E. Synthetic materials should be avoided in repairs to reduce the risk of empyema.

5. Which is the correct treatment for symptomatic paraesophageal hernia?
   A. Antacid therapy
   B. Iron supplements for anemia
   C. Antibiotic therapy for reflux pneumonitis
   D. Antiemetics for gastric bloat
   E. Surgical reduction

## ANSWERS

1. **Answer: D.** Most congenital diaphragmatic hernias can now be diagnosed on prenatal ultrasound and confirmed with chest x-ray or CT. These hernias are commonly associated with other congenital anomalies. A pH <7.15 is an indication for ECMO in a neonate with a Bochdalek hernia. Most patients with Morgagni hernias present with gastrointestinal distress in early adulthood. Mortality is directly related to the degree of pulmonary hypoplasia.
2. **Answer: E.** The most common scenario is a patient that sustains unilateral diaphragmatic paralysis from an iatrogenic injury. In this setting, there is no substantial morbidity and symptoms usually resolve within a year. Surgery is rarely required.
3. **Answer: C.** Anatomic findings, such as a large portion of the stomach in the chest, are not absolute indications for surgery. Failure of medical therapy and the development of reflux-associated complications such as aspiration pneumonitis, strictures, and Barrett's esophagus are all indications for surgery.
4. **Answer: B.** The majority of these tumors are discovered in the fifth to seventh decade of life. Most primary tumors are benign; however, the majority of diaphragmatic tumors are metastatic in origin and do not originate primarily from the diaphragmatic muscle. As a result, surgical resection is not usually indicated and is associated with poor outcomes. Synthetic materials are not associated with an increased risk of empyema.
5. **Answer: E.** A symptomatic paraesophageal hernia is an indication for surgical repair. Medical therapy has no role in the treatment of this condition.

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II

# ADULT CARDIAC SURGERY

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# 23 Cardiovascular Function and Physiology

*Jeffrey M. Dodd-o*

**KEY CONCEPTS**

- Membrane potentials are created by energy-dependent ion pumps that segregate charged ions on either side of hydrophobic cell membrane.
- Cell depolarization is possible because channels open within the hydrophobic membrane to allow charged ions, driven by concentration gradients, to cross the membrane.
- Trigger for the opening of transmembrane ion channel is typically a change in the membrane potential. Different channels are triggered to open at different membrane potentials.
- The sarcomere is the contractile element of the myocyte. Each sarcomere is composed of a series of parallel myofilaments. Coaxial movement of these myofilaments, some of which are tethered to the ends of the sarcomere, result in sarcomere shortening.
- The strength of contraction is influenced by resting length of the myocyte, sudden stretch of the myocyte, or rapidly repeated contraction of the myocyte. Speed of shortening is influenced by afterload.
- A ventricle exposed chronically to high afterload will adapt by concentric hypertrophy because this reduces wall stress according to Laplace's law.
- Myocardium receiving insufficient energy supply will die (infarction), become dysfunctional (ischemia), or reduce its energy needs (hibernate). Reperfused tissue is termed "stunned" if it does not contract up to its potential in spite of adequate energy supply.
- Diastole is more energy demanding than systole, and diastolic dysfunction can be more difficult to treat than systolic dysfunction.
- Dysfunctional endothelium leads to vascular occlusion by (1) exposing underlying tissue factor to circulating factor VII, initiating thrombosis, (2) not allowing for the interaction of thrombin with thrombomodulin and the subsequent activation of protein C to its anticoagulant form, (3) not producing nitric oxide, which is important to help decrease platelet activation, decrease vasospasm, and decrease vascular inflammation.

## BASIC MYOCYTE PHYSIOLOGY

### Physiology of the Myocyte Cell Membrane

The human body is composed predominantly of salts and water. This pool of salts and water is segregated into functional units (cells and their intracellular components) that locally alter the concentration of the salts they contain. Hydrophobic phospholipid membranes surrounding the cells (and intracellular compartments) regulate the exit/entrance of water-soluble salts and allow the cells to maintain this individualized environment (Fig. 23-1).[1] Units within these phospholipid membranes actively adjust the ion content within the cell (or intracellular compartment). For example, an energy-dependent sodium ($Na^+$), potassium ($K^+$) pump extrudes $Na^+$ ions from the cell and takes $K^+$ ions into the cell at an exchange of three $Na^+$ ions extruded per two $K^+$ ions taken in. This allows cells to raise intracellular $K^+$ concentrations and lower intracellular $Na^+$. Another pump extrudes calcium ($Ca^{2+}$) in exchange for $Na^+$. This decreases $Ca^{2+}$ concentrations in the intracellular (compared with the extracellular) fluid, but allows $Na^+$ to reenter the cell. This pump is driven by the $Na^+$ gradient created by the energy-dependent $Na^+$, $K^+$ pump. Other channels within the membrane act as passages that intermittently open to allow transit of a specific ion through the cell membrane. Regulation of pump activation and channel opening is vital for the proper functioning of the cell. Similarly, intracellular compartments called the sarcoplasmic reticulum (SR) contain energy-dependent ion pumps

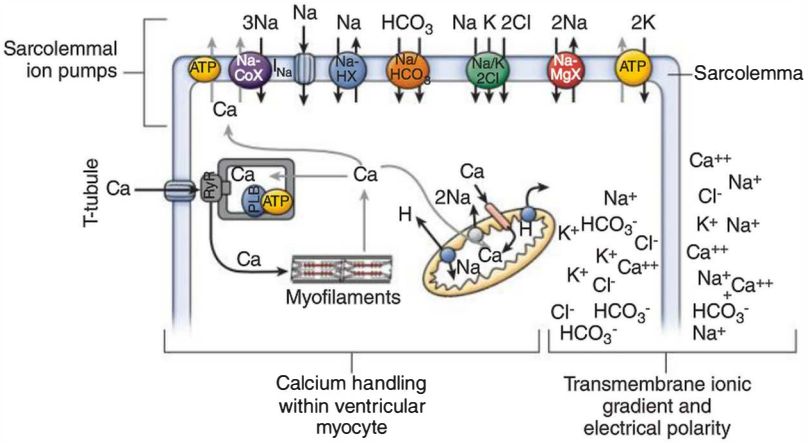



**FIGURE 23-1** Sarcolemmal ion pumps, the transmembrane concentration gradient, and electrical polarity they create, as well as calcium transport in ventricular myocyte. PLB, phospholambam; RyR, Ryanodine receptor; X, Exchanger. (Modified with permission from figure 1b, p 898, Bers DM et al., *Cardiovascular Research* 2003;57:897–912. Copyright Oxford University Press.)

in their surrounding membranes that allow them to collect the majority of the intracellular $Ca^{2+}$. Moving ions against their concentration gradient to create a relative intracellular deficit or abundance requires energy. In the cell, this energy is supplied in the form of adenosine triphosphate (ATP).

## Myocyte Depolarization

Relative to the extracellular fluid, the intracellular fluid in the resting state has a lower ratio of positively to negatively charged ions (i.e., the myocyte membrane is polarized). These electrical and ionic gradients across the myocyte membrane when at rest create the potential for rapid ionic shifts if restrictions to ion movement across the membrane are relaxed. Transmembrane ion movement is facilitated by a series of events precipitated by a small decrease in the magnitude of the electrical polarity across one point of the myocyte membrane. The resultant ion shifts increase calcium concentrations at critical intracellular sites, allowing myocyte contraction.[2]

When the transmembrane electrical potential, –90 mV, at rest, becomes less negative (i.e., depolarizes), sodium channels on the cell membrane are triggered to open (Fig. 23-2). Some of these sodium channels are also triggered at the time of membrane depolarization to close, although the onset of closure is (of course) delayed until after the channel has been opened. Other channels, like L-type calcium channels, also open when the cell membrane depolarizes. The initiation of ion passage through calcium channels is delayed until after the $Na^+$ channels have begun to close. The opening of these $Na^+$ and $Ca^{2+}$ channels results in the entrance of cations into the cell, decreasing the magnitude of the membrane potential. As the membrane potential reaches a nadir, $K^+$ channels are triggered to open. Their opening increases the rate of exit of $K^+$ from the intracellular space into which it had been concentrated. The loss of cations from the intracellular space helps return the transmembrane potential back to the resting state. This $K^+$ channel is inwardly rectified (i.e., turned off when cell is depolarized) and is responsible for maintaining the resting membrane potential. This basic sequence is somewhat modified by channels for $Cl^-$ and transiently open channels for $K^+$ (activated after depolarization to allow $Cl^-$ entrance into cell and $K^+$ efflux from cell, beginning to reverse to return the transmembrane potential toward –90 mV).

As a new transmembrane electrical gradient develops at one point on the sarcolemma (i.e., membrane of a muscle fiber), ion channels traversing the adjacent sarcolemma, closed to the passage of ions under resting transmembrane potentials, become exposed to the new transmembrane potential of the adjacent sarcolemma. This exposure increases the open probability of the nearby channels. The passage of ions through these newly open channels changes the membrane potential surrounding the channel, exposing an additional section of the cell membrane to a different transmembrane potential. In this way, the new transmembrane potential propagates along the surface of the myocytes.

The trigger to opening the sarcolemmal ion channels is often the potential or ionic concentration gradient of the surrounding milieu. Thus, transmembrane channels are frequently described as being either voltage-gated (opening probability is increased if the transmembrane potential of the surrounding membrane is within certain parameters) or ion-gated (opening probability is increased if there is a sudden change in the concentration of an ion in the surrounding fluid). Some channels, described as rectified channels, alter the resistance imposed by the channel-to-ion flow through the channel as the surrounding electrical or ion potential is changing. Speaking of $K^+$ channels, an ion whose exit from the depolarized cell tends to restore the resting membrane potential (by increasing the relative concentration of negatively charged ions intracellularly), outward rectified channels increase the

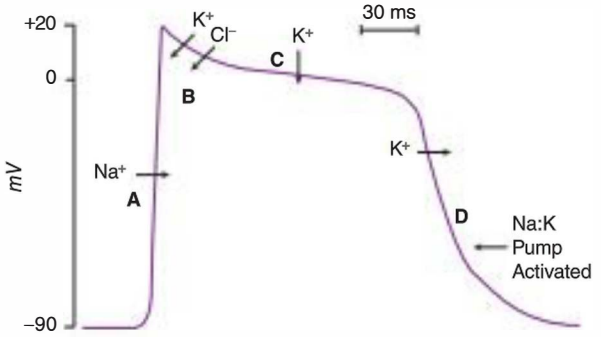



**FIGURE 23-2** Correlation between the changes in ion conductance and the resultant changes in transmembrane potential during the various phases of the cardiac myocyte action potential. A, depolarization; B, rapid repolarization; C, plateau phase; D, late repolarization. (Modified from Rubart M, Zipes DP. Mechanisms of sudden cardiac death. *J Clin Invest* 2005;115(9):2305–2315. With permission.)

resistance to $K^+$ passage as the membrane potential returns to resting state. This type of channel tends to promote restoration of the repolarized state. By contrast, inward rectifying $K^+$ channels are relatively more resistant to ion passage as the membrane is depolarized. This type of channel tends to promote the maintenance of the depolarized state (Fig. 23-2).

## T Tubules and Sarcoplasmic Reticulum

T tubules are invaginations in the cell membrane that penetrate into the cell to lie in close proximity to the myocyte contractile proteins. These T tubules act as extensions of the surface membrane and allow changes in the cell surface to effect changes deep within the myocyte.

Compared with the membrane on the surface of the cell, the membrane of T tubules has a relatively high concentration of L-type calcium channels. These T tubules extend to close approximation with the myofibrils—the contractile apparatus of the myocyte. Also located intracellularly near the junction of the myofibrils and the T tubules are compartments known as SR. The membrane of the SR contains ion pumps that both concentrate calcium within the SR and channels that, when open, allow the sequestered calcium to exit the SR. The stimulus for opening of the calcium channels on the SR is a rise in calcium in the cytoplasm surrounding the SR. Thus, as membrane depolarization propagates from the cell surface down the invaginations known as the T tubules, it stimulates L-type calcium channels in the T tubules to open. This allows calcium to enter the cell at a site near the SR, raising cytosolic calcium concentrations near the SR. These high calcium concentrations near the SR stimulate calcium release from the SR, a phenomenon known as calcium-induced calcium release. The rise in calcium concentrations near the myofibrils reorients the troponin in the thin filaments, moving the tropomyosin (attached to the troponin) and making it sterically possible for the actin of the thin filament to bind to myosin. Contraction follows. Contraction is terminated (and relaxation initiated) by the closing of calcium channels in the SR and the reuptake of calcium by the SR as a result of pumps activated on the SR. This reduces calcium concentrations surrounding the thin/thick filaments, so tropomyosin filaments return to a position preventing the interaction of actin and myosin filaments.

## Regional Differences in Cardiac Myocyte Depolarization

The ion channel(s) predominating in cardiac myocytes differ by the myocyte's location in the heart (atria/ventricles vs sinus node/AV node) (Fig 23-3).[3] This difference in predominating ion channel(s) helps explain the special features of different sites of the heart. Fast-conducting sodium channels predominate in the atria and ventricles, allowing for rapid depolarization and expediting conduction. These channels are less prominent in the SA node and AV node, reducing rate of conduction through these sites.

Additional features of the SA and AV node are responsible for the automaticity (i.e., spontaneous depolarization) that is characteristic of these cells. The resting membrane potential of contracting atrial and ventricular myocytes is maintained by an inward rectifying (i.e., shuts off when cell is depolarized) potassium channel that maintains resting membrane potential of around –90 mV. In the nodal tissues, additional channels (voltage-dependent slow Na channel that allows Na to slowly enter cell as depolarization reaches –70 to –90 mV and, possibly an outward rectifying K channel that reduces K flow as repolarization progresses) result in an unstable "resting" membrane potential. Thus, the resting membrane potential of nodal cells will spontaneously diminish from about –70 to –50 mV, at which time voltage-dependent $Ca^{2+}$ channels will open and allow complete depolarization.

Finally, nodal tissue (predominantly AV node) contains a $K^+$ channel that is central to pharmacologic interventions commonly used to treat dysrhythmias. This channel, activated by adenosine and acetylcholine ($I_{Kach,Ado}$), allows $K^+$ to exit the cell upon stimulation by either adenosine or acetylcholine. The exit of $K^+$ makes the membrane potential more negative, hyperpolarizing the cell and making depolarization more difficult. Thus, acetylcholine reduces sinus node spontaneous depolarization and adenosine blocks transmission through the AV node.

## Excitation: Contraction Coupling

The cascade of events linking myocyte membrane depolarization to myocte contraction is termed excitation:contraction coupling. It can be summarized as follows (Figs. 23-2 and 23-3):

Phase 1 depolarization, mediated by opening of voltage-gated fast Na channels, depolarizes the membrane to a point at which L-type $Ca^{2+}$ channels can open (Fig. 23-3). The influx of calcium through these (dihydropyridine-sensitive)

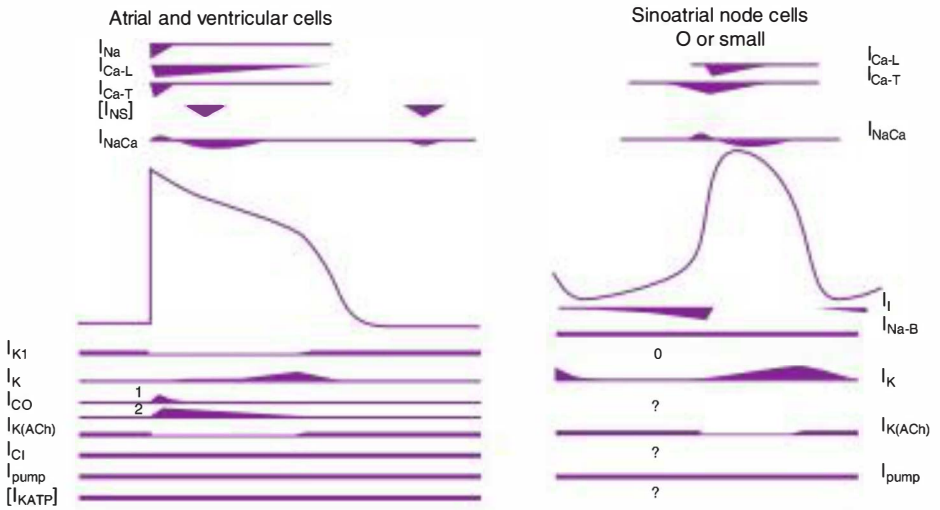



**FIGURE 23-3** A comparison of the stylized action potential of atrial and ventricular cells (left) vs sinoatrial node cells (right) as well as the ionic currents whose contribution to each action potential is confirmed. Other ion channels may exist. Ion current bar deflections depict only the approximate time course (not the magnitude) of the current. Brackets around channel names indicate the current is active only under pathologic conditions. Question mark indicates the uncertain presence of this channel in the sinoatrial node. $I_{NS}$, calcium-gated channel, sodium inward current; $I_{NaCa}$, electrogenic $Na^+$–$Ca^{2+}$ exchange current; $I_{K(ACh)}$, acetylcholine-dependent potassium current; $I_{NS} = I_{Cl}$, chloride current; $I_{pump}$, electrogenic pump; $I_f$, sodium-dependent inward current; $I_{Na-B}$, inward background sodium current. (Reproduced with permission from Sicilian Gambit: A report of the Task Force of the Working Group on Arrythmia of the European Society of Cardiology. *Circulation* 1991;84:1831–1851, P1835, Figure 2. Copyright Wolters Kluwer Health.)

voltage-gated channels, especially through those located along the T tubules, increases intracellular calcium concentration in the vicinity of the SR. (The calcium channels on the SR are termed ryanodine-sensitive calcium channels because the compound ryanodine induces their opening.) This triggers the opening of calcium channels in the SR membrane, releasing calcium stored in the SR. The result of calcium entrance into the cell via L-type calcium channel opening, combined with release of calcium from SR stores, is a dramatic increase in calcium concentration surrounding the contractile myofilaments. High concentrations of calcium allows binding of calcium to troponin C of the thin filament, modulating the troponin such that tropomyosin (attached to troponin) gets moved from its position of preventing interaction between actin (of the thin filament) and myosin. The strength of bond between actin and myosin is decreased by acidosis, high concentrations of $Mg^{2+}$, or high concentrations of phosphate. This bond is enhanced by caffeine and β-adrenergic stimulation. β-Adrenergic stimulation increases actin–myosin bonding through a cascade that results in the activation of myosin-binding protein C.

## Regulation of Myocyte Function by the Myocyte Cell-Surface Receptor

### BETA RECEPTORS

The beta receptor is a protein that is incorporated within the cell membrane. It spans the entire depth of the membrane. It has both components that extend into the cytoplasm and components exposed on the surface of the cell.[4] When an extracellular agonist stimulates the portion of the receptor exposed on the cell surface, a conformational change in the beta receptor allows the portion of the receptor protruding into the cytoplasm to bind to a G protein (i.e., it is a G protein-coupled receptor). G proteins have multiple components, and stimulation of the G protein causes dissociation of the subunits so that each subunit is free to regulate its particular effector. One such effector is adenylatecyclase, which is activated to increase intracellular concentrations of cyclic adenosine monophosphate (cAMP) and thereby activate protein kinase A (PKA). Activated PKA is then capable of phosphorylating multiple intermediaries of excitation:contraction. For example, it increases intracellular calcium concentrations by facilitating calcium entrance into the cell (via L-type calcium channels) as well as calcium release from compartments within the cell (i.e., the SR).

β-Agonist stimulation also expedites relaxation. Relaxation results when cytosolic calcium is in low concentration or is prevented from binding to troponin C. If troponin C is not bound to calcium, tropomyosin returns to a location that inhibits interaction between actin and myosin. Cytosolic calcium content drops when calcium leaves the myocyte through the sodium–calcium exchanger on the cell surface. The predominant method of lowering cytosolic calcium levels, though, is reuptake by the SR. The pump mediating calcium reuptake by the SR is dependent on ATP and regulated by the phosphorylation of phospholamban. Beta stimulation facilitates relaxation by two mechanisms. First, it

results in phosphorylation of troponin I by PKA, expediting dissociation of calcium from troponin C. Beta stimulation also results in phosphorylation of phospholamban, which speeds up calcium reuptake into the SR.

### MUSCARINIC RECEPTORS

Muscarinic receptors sensitive to acetylcholine are also present on the myocardium. In particular, the heart contains the M2 subtype of muscarinic receptor.[5] Like beta receptors, muscarinic receptors are G protein-coupled, which are incorporated within the cell membrane, span the entire depth of the membrane, and contain components exposed to both the extracellular fluid and the intracellular fluid. The G protein to which the M2 receptor is coupled has inhibitory effects on adenylatecyclase and is sensitive to pertussis toxin. In fact, the negative inotropic effects of M2 receptor stimulation appear to be indirect; that is, they can be demonstrated only in the setting of baseline stimulation adenylatecyclase. Therefore, it appears that their negative inotropy results entirely from this inhibitory effect on adenylatecyclase.

In the atria and nodal myocytes, M2 receptors appear to have a direct effect (i.e., not dependent on baseline stimulation) on the inward rectifying potassium channel that maintains phase 4 (resting) membrane potential. By opening this channel through a direct action of the G protein upon the channel, M2 receptor stimulation hyperpolarizes the resting membrane to slow the automaticity rate of the cells.

### ADENOSINE RECEPTORS

Adenosine receptors are also G-coupled protein receptors. There are three basic subtypes of adenosine receptors ($A_1$, $A_2$, $A_3$). $A_1$ and $A_3$ subtypes inhibit adenylatecyclase via inhibitory G proteins whereas $A_2$ receptors increase adenylatecyclase via stimulatory G proteins.[6] These receptors also regulate other pathways via G proteins. Thus, $A_1$ and $A_3$ subtypes mediate the catabolism of phospholipids whereas $A_2$ receptors regulate phosphoinositide metabolism.

Two clinical effects of exogenous adenosine can be traced back to the distribution and effects of various adenosine receptors. $A_1$ receptors are plentiful in the nodal tissues. $A_1$ receptor stimulation opens the inward rectifying potassium channel that maintains phase 4 (resting) membrane potential. Like the effects of M2 receptor stimulation of this channel, opening inward rectifying potassium channels via $A_1$ receptor stimulation hyperpolarizes the resting membrane to slow the automaticity rate of the cells. In the coronary vasculature, $A_2$ receptors predominate. Their stimulation results in vasodilation, likely through G protein–mediated activation of intracellular adenylatecyclase.

### α-ADRENERGIC RECEPTORS

There is growing evidence that α-adrenergic stimulation of myocytes results in a positive inotropic effect.[7] The mechanism and clinical importance of this is unclear. It may also be coupled to myocardial hypertrophy.

## MYOCARDIAL CONTRACTILE FUNCTION

Cardiac myocytes possess the capacity to contract because they contain a series of protein filaments (myofibrils) oriented along the longitudinal axis of the cell (see later). For myocytes to shorten, these longitudinally oriented myofibrils must interact with each other and slide along each other in the longitudinal axis. A rise in intracellular (cytosolic) calcium is critical for this myofibril interaction. Calcium enters the cytosolic space from two sources. First, extracellular calcium crosses the plasma membrane to enter the cell. This rise in intracellular calcium then induces the release of calcium, the second source—intracellular calcium storage pools (calcium-induced calcium release). At baseline, extracellular calcium concentrations are higher than intracellular calcium concentrations because calcium is actively extruded across the cell's phospholipid plasma membrane. The entrance of calcium back into the cell (across the plasma membrane) is a passive process, driven by the concentration gradient and allowed by the brief opening of channels through the calcium-impermeant phospholipid plasma membrane. The impetus for the stimulation is a change in the transmembrane electrical gradient (see Myocyte Cell Membrane Physiology section).

### The Sarcomere as a Contractile Element

#### CONTRACTILE APPARATUS

The sarcomere is the contractile unit of the myocyte. A sarcomere contains two types of coaxially aligned filaments that differ in their component protein (actin/tropomyosin/troponin vs myosin) as well as in thickness (actin/tropomyosin/troponin filaments are thinner, myosin filaments are thicker). Thin and thick filaments are arranged as follows. Each thin filament is axially aligned with, but not attached to, another thin filament. Each pair of thin filaments is straddled by a single thick filament lying parallel to it. Within the myocyte, the contractile unit (a pair of thin filaments and their associated thick filament) is bound on the ends by a Z band (Fig. 23-4). The Z band (for *Zuckung*, the German word for "contraction") is a dark band visible by electron microscopy and corresponding to the site to which the ends of a series of parallel thick and thin myosin filaments are anchored. This defines the ends of a sarcomere. Under appropriate stimulation, the members of an axially aligned thin-filament pair will move closer to each other through an interaction with the thick filament that straddles them. Because each member of a thin filament pair is anchored to Z bands, this coaxial movement draws the Z bands within the cell closer to one another, shortening the cell.[1,8]

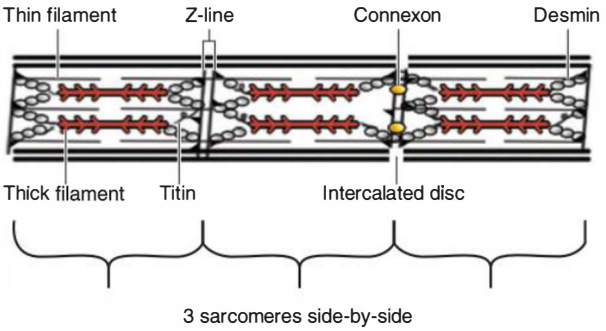



**FIGURE 23-4** Depiction of three sarcomeres located side-by-side. Each sarcomere is depicted with three pairs of axially aligned thin filaments. Each of these three pairs is separated from each other by a thick filament. The filaments are maintained in the proper alignment by desmins, which act as scaffolding. Each thin filament is anchored at one end to the Z-line, with the other end extending centrally into the sarcomere. The connexons are channels between neighboring sarcomeres that allow signals between sarcomeres to be communicated.

Each end of the thick myosin filament is attached to the Z band by a protein called titin or connectin. This protein contains a nonmalleable portion that anchors the filament to the Z band as well as a distensible portion that enfolds on itself if the sarcomere is not stretched. As the sarcomere stretches, the Z bands are pulled farther apart from one another and the enfolded portion of the titin protein is extended. When stretching is relieved, the elastic recoil of the titin molecule helps to actively restore the sarcomere to its resting length.

The movement of thin filaments is an energy-requiring process regulated by local calcium concentrations within the cell. Two thin filaments move toward each other in the axial plane by each "pulling" itself along a shared myosin filament. Under "resting" conditions, physical contact between actin and myosin filaments is prohibited by the tropomyosin component of the thin filament. Tropomyosin is a protein strand that can interdigitate between actin and myosin, preventing their physical contact. Tropomyosin can be moved out of place by the actions of the third protein of the thin filament, the troponin protein. The presence of calcium sterically alters the troponin, causing it to reorient itself within the thin filament and thereby move the tropomyosin strand to which it is attached. The movement of the tropomyosin strand removes the physical barrier preventing actin–myosin interaction and allows the thin filaments to move closer to each other along a shared myosin chain.

## Myocardial Contractile Physiology

Contractility is the ability of a myocyte to shorten, measured at a given preload and a given afterload. Changing the preload will alter contractility due to the length–tension relationship. Changing the afterload will alter contractility because it mandates generation of a different wall stress to achieve shortening.

### LENGTH–TENSION (FRANK–STARLING) RELATIONSHIPS

The force of contraction of a cardiac myocyte increases when the sarcomere is stretched (within the lengths of 1.7–2.4 μm).[9] Mechanistically, this increased contractility can be divided into two parts: (1) an immediate increase in force that is unaccompanied by a change in intracellular calcium concentration and (2) an additional increase in force of delayed (minutes) onset that is associated with an increase in intracellular calcium.[10] The increase in intracellular calcium causing the second phase is probably mediated by changes in the cell membrane. The first phase, which apparently involves a change in myofilament sensitivity to calcium, is the Frank–Starling phenomenon (named for Otto Frank and Ernest Starling, who initiated the concept based on experimental findings they made at the beginning of the 20th century). It was originally hypothesized that sarcomere stretching improved myosin–actin cross-bridge formation. However, the increase in contractile force is observed even if the sarcomere is stretched to distances that would begin to reduce the potential for actin and myosin crossbridge formation. An alternative explanation is that stretching the myocyte narrows the sarcomere, reducing the spacing between myosin and actin filaments. This facilitates myosin–actin interaction. Studies in which the interfilament distance is reduced by cellular dehydration result in an increased calcium sensitivity of contractile strength, similar to that seen with myocyte stretch. A yet unexplained mechanism of stretch-induced change in myofilament sensitivity to calcium remains a third possible explanation.

### FORCE–VELOCITY RELATIONSHIPS

To measure contractile force free of compounding influences from preload, afterload, or heart rate, the concept of measuring the velocity of shortening in a myocyte with no afterload has been developed.[11] In such a scenario, the maximal velocity of shortening ($V_{max}$) would be a measure of the inotropy of a myocyte. Practically speaking, it is difficult to completely remove external resistance from a contracting myocyte. The value of $V_{max}$ must therefore be extrapolated from the maximal velocities observed when a myocyte is made to contract against a series of different afterloads. At one extreme of this series would be the minimal afterload at which the myocyte is no longer able to shorten at all ($V_{max} = 0$). This relationship is hyperbolic rather than linear (Fig. 23-5). Although the reason for this hyperbolic relationship remains unclear, it is felt to be due in part to shortening inactivation and in part to elastic forces that passively resist stretch (at long sarcomere length) or shortening (at short sarcomere length). Such passive elastic forces could be contributed by titin.

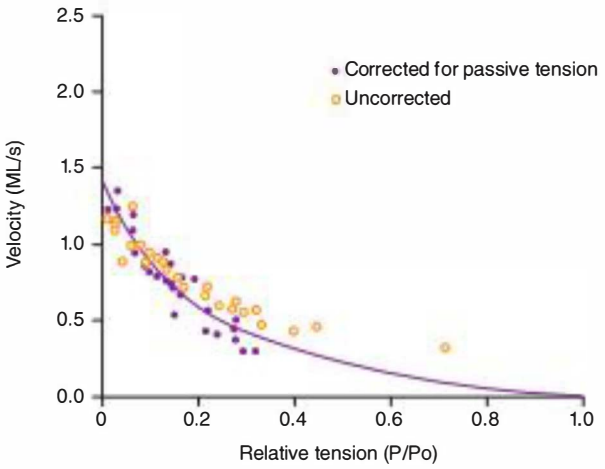



**FIGURE 23-5** The influence of resting tension on the shortening velocity of isolated myocytes. The general relationship of faster shortening velocity observed when resting external tension is decreased can be seen whether passive (intra-myocyte) tension is present (open circles) or mathematically excluded from the calculations (closed circles). (Figure 7 from Sweitzer NK, Moss RL. Determinants of loaded shortening velocity in single cardiac myocytes permeabilized with alpha-hemolysin. *Circ Res* 1993;73:1150–1162, with permission. Copyright Wolters Kluwer Health.)

## "Anrep Effect"

This is a two-phase response of myocytes to an abrupt stretch.[12] The first phase is the Frank–Starling effect—an increase in contractility, which occurs without a change in cytosolic calcium. There is a delayed second phase, which is associated with an increase in cytosolic calcium. The change in intracellular calcium seems to be independent of the SR, although the exact mechanism behind the rise remains obscure.

## "Treppe Effect"

The Treppe effect (*Treppe*, German for "step") is the observed increase in strength of contraction when heart rate is increased. It is associated with an increase in intracellular calcium concentrations,[10] which itself may be due to an inability of the SR and myocyte calcium-extruding pumps to completely return cytosolic calcium to baseline levels between sequential cell depolarizations. The Treppe effect may also be influenced by endocardial–myocyte cross-talk through a process involving endothelin-I.

# CARDIAC PUMP FUNCTION

## Myocyte Cytoskeleton

Synchronized contraction of cardiac myocytes is necessary for most efficient pumping function of the heart.[8] It requires tight adhesion of cells along the axis of their shortening as well as organized propagation of the contractile stimulus. To accomplish this, the basic structure of the myocyte is one of contractile myofibrils attached via fascia adherens to cadherin anchors at the ends of the myocyte (Fig. 23-4). The myofibrils are held in alignment by an intracellular scaffold-like network consisting of the protein desmin. These desmin "scaffolds," traversing the myocyte at intervals along its longitudinal axis, are anchored to the lateral sarcolemmal wall by plaques called costameres. These plaques, rich in the protein vinculin, act both to maintain the spatial interval between the desmin scaffolds and to mechanically link the cells laterally to the sarcolemmal membrane and extracellular matrix. The desmins are anchored to the cadherins at the longitudinal end of the myocyte by desmosomes.

The site of end-to-end adherence between two myocytes is called the intercalated disk. This site physically anchors two myocytes and allows for chemical signaling and intercellular continuity of action potential propagation between these myocytes. The physical anchor is maintained by junctions between cadherins of adjacent cells. Communication between myocytes connected in the longitudinal axis is made possible by channels. Each channel comprises two connexons aligned coaxially. Each connexon comprises six connexin molecules arranged in a circle. There are different types of connexin and different densities of connexon channels among different myocytes.

The characteristics of these intercalated disks are quite important in determining the ease of communication between myocytes in the longitudinal plane. Consistent with this, the composition and number of connexons varies with the electrophysiologic requirements of the myocytes involved. Myocytes of the atria and ventricles, serving principally a contractile function, contain a fair abundance of connexon channels, with connexin 43 being the most abundant connexin present. Cells of the sinus node and atrioventricular node contain few connexon channels joining cells longitudinally. The sparcity of connexon channels in the sinus node allows the natural depolarization of the cells to occur without inhibition by the hyperpolarizing effects of the surrounding contractile myocytes. The sparcity of these channels in the atrioventricular node slows communication between cells, slowing transmission of the electrical impulse. By contrast, the cells of the Purkinje system contain high numbers of large connexon channels composed of the high-conductance connexin 40. This allows rapid transmission of electrical impulses throughout the Purkinje system.

## Cardiac Mechanics

### FRANK–STARLING MODEL

The ability of the heart to contract is influenced by the resting volume within the heart. This is analogous to the way the contractility of the sarcomeres (and myocytes) composing the heart is influenced by the resting length to which they are stretched. Physiologists therefore view the heart as a series of

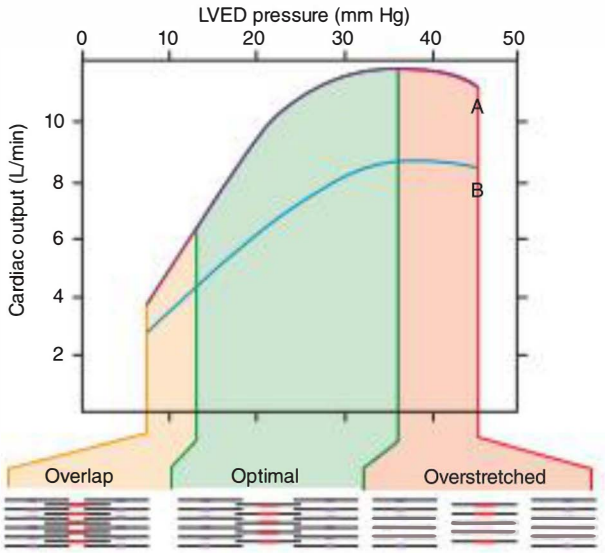



**FIGURE 23-6** Frank–Starling Ventricular Function Curve in normal heart. Top: As depicted in Curve B, an increase in left ventricular end diastolic pressure (LVEDP) increases the volume ejected by the heart. Alternatively, the volume ejected at any given LVEDP can be increased by increasing the inotropic state of the heart (i.e., moving from Curve B to Curve A). Bottom: Increasing the LVEDP stretches the actin:myosin filaments. (Instructors Resource CD ROM to accompany *Porth's Pathophysiology: Concepts of Altered Health States*. 7th ed. With permission. Copyright Lippincott, Williams and Wilkins, 2005.)

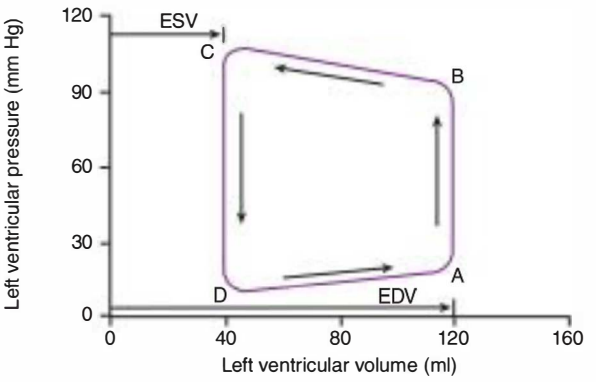



**FIGURE 23-7** Schematic depiction of left ventricular pressure–volume relationship. A, end-diastole; upward arrow, isovolumetric contraction; B, aortic valve open; leftward arrow, ventricular ejection; C, aortic valve closure; downward arrow, isovolumetric relaxation; D, mitral valve opening; rightward arrow, diastolic ventricular filling. (Reproduced with permission from Pagel PS, Grossman W, Haering JM, Warltier DC. Left ventricular diastolic function in the normal and diseased heart. Perspectives for the anesthesiologist. *Anesthesiology* 1993;79:836–854. Copyright Wolters Kluwer Health/Lippincott Williams & Wilkins.)

sarcomeres demonstrating length–tension relationships—the model conceptualized by Frank and Starling (Fig. 23-6). In this regard, the capacity of the heart to eject blood against a given resistance increases as the volume within the heart immediately prior to initiating systole (i.e., the end-diastolic volume) increases. This relationship, and its analogy to the length–tension relationship of individual sarcomeres, is demonstrated in Figure 23-6. Because the volume within equally compliant hearts is directly proportional to the pressure within the heart, this Frank–Starling model can also be displayed as an effect of pulmonary capillary wedge pressure on the stroke volume or ejection fraction of the left ventricle (LV).

## PRELOAD AND DIASTOLIC COMPLIANCE

Diastole is the return of the ventricle to the maximal degree of distention it will achieve prior to initiating another contractile effort. This is a two-step process—the passive recoil of previously contracted myocytes followed by the active distension of these myocytes by external forces. In the first step, cessation of contractile efforts by myocytes allows these myocytes, after contracting to a length less than their resting length, to return to their resting length much in the same way that a compressed spring returns to its resting length after contracting forces are removed from it. The ease and extent of recoil is inversely proportional to the amount of fibrosis between the myocytes.

In the second step, filling the ventricular chamber with blood distends the ventricle, stretching the individual sarcomeres of the component myocytes. The magnitude of force required to stretch a sarcomere to a given length varies with the distensibility of the sarcomere (analogous to stretching a spring) and the fibrosis between myocytes. Analogously, the magnitude of the three-dimensional force (i.e., pressure) needed to distend the ventricular chamber to a given volume varies with the compliance of the chamber (Fig. 23-7). Distending two ventricles with the same volume of blood will result in a higher intraventricular pressure within the less compliant ventricle. Furthermore, the compliance of a chamber changes as it fills. Adding 20 mL to a ventricle increases the intraventricular pressure much less when the ventricle is nearly empty than when it already contains 200 mL of blood.

## AFTERLOAD

Under normal circumstances, the pressure preventing a ventricular chamber from contracting (i.e., afterload) is the pressure required to sufficiently distend an arterial bed to accept the blood ejected by the contracting ventricle. Thus, the afterload to the LV is the pressure within the systemic arterial system. As with all elastic chambers, the compliance of the arterial bed decreases as it fills with blood. Thus, the afterload of the LV increases as the ventricle empties and ejects blood into the aorta. At some point, the ventricle stops ejecting because the pressure required to further distend the systemic arterial system exceeds that which the ventricle is capable of generating. This point marks the end of physiologic ventricular systole.

## THE CARDIAC CYCLE

***Pressure–Volume Loops.*** The above discussion emphasizes three points: (1) the extent to which ventricular contractility is facilitated by optimizing sarcomere length at a given point in its pressure-generating cycle is reflected by the effect on strength of contraction of changing the intraventricular volume at that point during systole, (2) LV compliance is reflected by the pressure generated within the LV for any increase in LV volume during relaxation, and (3) the capacity of the LV to eject blood depends on its ability to generate enough pressure to overcome afterload. This illustrates the utility of evaluating ventricular performance in terms of the relationship between the pressure ($x$-axis) and volume ($y$-axis) within the ventricle at any point in time.

Active contraction of the ventricle is indicated by the bottom right-hand corner of the pressure–volume square (Fig. 23-8). At this point, intraventricular volume stops increasing (marking the end of diastole) and intraventricular pressure begins to rise rapidly. At the top right-hand corner of this relationship, the aortic valve opens. Thus, by generating a constant pressure just strong enough to keep the aortic valve open, the ventricle is able to continually eject blood into the aorta. The volume within the ventricle thereby decreases, myocytes subsequently contract, and the sarcomere shortens from its ideal length for force generation. At some point, the ventricular sarcomeres have shortened so much that they are no longer able to generate the force needed to further contract. This point, indicated by the top left-hand corner of the pressure–volume loop, is termed the end-systolic pressure–volume point and represents the dependence of ventricular shortening on the volume of the LV and its capacity to generate pressure. From this point, the myocytes cease generating force and the intraventricular pressure decreases (represented by the vertical line marking the left side of the pressure–volume loop). Finally, the mitral valve opens and blood starts filling the ventricle. Although the ventricle has not yet begun to contract, the pressure within it slowly increases as blood enters across the mitral valve prior to initiation of myocyte shortening.

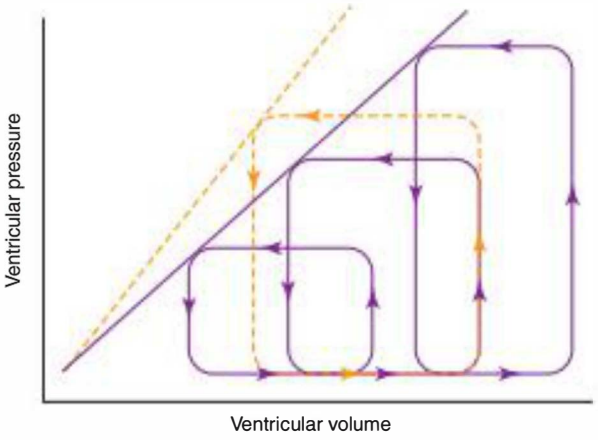



**FIGURE 23-8** The Frank–Starling law of the heart–end-systolic pressure is determined by end-systolic volume and is independent of end-diastolic volume. The end-systolic pressure–volume relationship is altered by the ventricular contractile state. As indicated by dashed line, increased inotropy increases the ejection volume and end systolic pressure at any given end-diastolic ventricular volume. (Reproduced with permission from Konhilas JP, Irving TC, de Tombe PP. Frank-Starling law of the heart and the cellular mechanisms of length-dependent activation. *Pflugers Arch* 2002;445(3):305–310. Copyright Springer.)

***Contractility.*** As indicated above, the end-systolic pressure–volume point on the pressure–volume loop indicates the limit to the pressure-generating capacity of the ventricle at a given preload. By changing the afterload experimentally, a series of pressure–volume loops can be generated such that the minimal preload required to generate any given pressure can be determined. The straight line connecting the end-systolic pressure–volume points of this series of loops is termed the end-systolic pressure–volume relationship (ESPVR). This relationship is an indication of the strength of contraction of the ventricle. A more vertical line or one shifted more to the left indicates greater contractility. A more horizontal line or one shifted more to the right indicates less contractility.

***Compliance (Fig. 23-9).*** Similar to its usefulness in evaluating LV contractility, the pressure–volume loop can be used to monitor the diastolic function of the heart. The bottom right corner of the pressure–volume loop marks the point at which diastole ends and systole begins for the ventricle. This point, the end-diastolic pressure–volume point, indicates the pressure required to fill the relaxed ventricle with the volume of blood it contains at end-diastole. A series of pressure–volume loops can experimentally be created to evaluate the pressure generated within the relaxed heart as it is filled with greater or lesser volumes of blood. The line connecting the end-diastolic pressure–volume points of this series of loops is termed the end-diastolic pressure–volume relationship (EDPVR). Unlike the ESPVR, the EDPVR tends to be curvilinear because the compliance of elastic containers tends to decrease as the container is filled. Nevertheless, an EDPVR line that is more vertical or raised higher along the vertical axis suggests decreased compliance of the ventricle. An EDPVR line that is more horizontal or lowered along the vertical axis suggests an increased compliance of the ventricle.

## MYOCARDIAL WALL STRESS

A circular object is envisioned as a series of 360 straight lines each offset from one another by 1 degree and each tangential to the radius of the circle. The stress on the wall of a distended, elastic circle can then be viewed as the force distending each of these tangential lines. In the case of the heart, the stress on the wall of the ventricle can be thought of as the force stretching each of the myocytes of the wall.

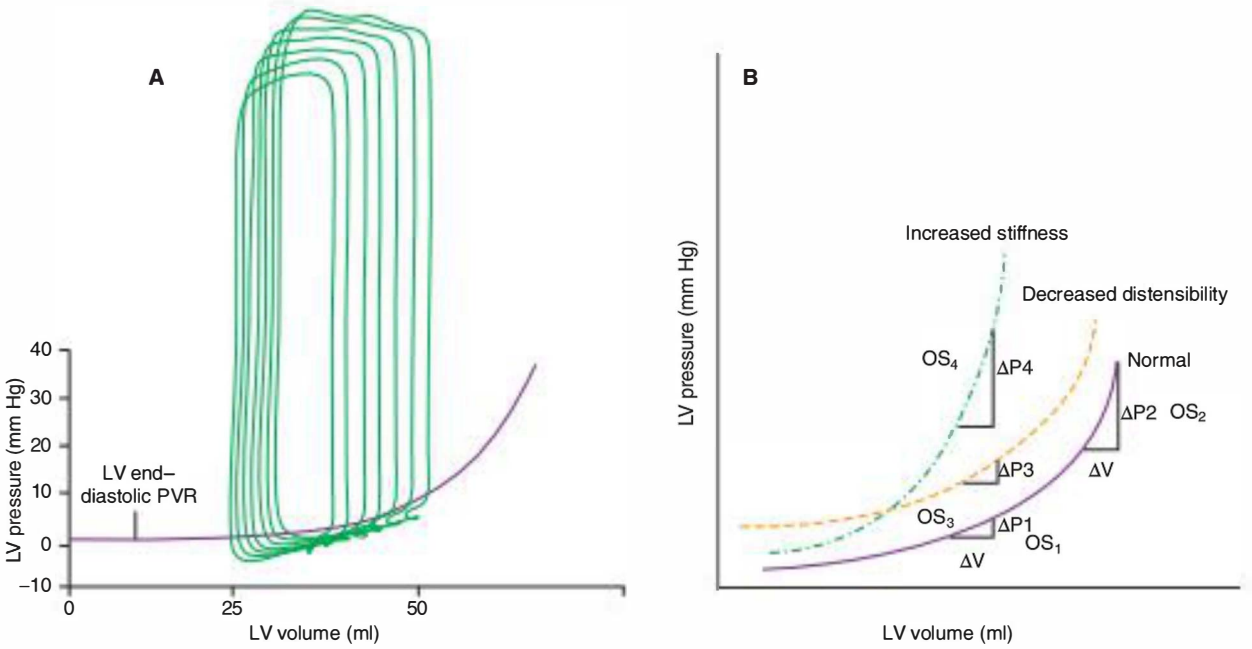



**FIGURE 23-9** **A.** Determining left ventricular compliance by changing left ventricular volume to define end-diastolic pressure–volume relationship (EDPVR). The curvilinear nature of EDPVR suggests that normal LV becomes more resistant to filling as end diastolic volume increases. **B.** Illustration of the effect of different left ventricular operant stiffness (OS) conditions on EDPVR. Increasing slope of EDPVR suggests decreasing compliance of myocardium/intercellular components; decreasing slope of EDPVR suggests lusitropy; parallel shift up of EDPVR (with same slope) suggests extramyocardial forces (RV loading/interventricular forces; pericardial constraint). (Reproduced with permission from Maniu CV, Redfield MM. Diastolic dysfunction: Insights into pathophysiology and pharmacotherapy. *Expert Opin Pharmacother* 2001;2:997–1008.)

The interrelationship of the factors composing this force is a physical principle explained by the law of Laplace. This law states that the tension in the wall is related to the pressure gradient across the wall (P), the radius of the ventricle (R), and the wall thickness (th) as follows (Fig. 23-10):

$$T = [(P)(R)]/[(2)(th)]$$

Thus, distending the ventricle (increasing the radius *R*) increases the stress on the ventricular myocytes. By contrast, hypertrophy of the ventricle (increasing wall thickness th) decreases tension on the wall. This explains why ventricular hypertrophy is a natural adaptation of the LV to hypertension.

## CARDIAC ENERGETICS

Molecules consist of positively charged protons and negatively charged electrons in close proximity. This close proximity is made possible by electromagnetic force or "bonds" between the positively and negatively charged particles. According to the first law of thermodynamics, the energy of these bonds must be converted to another form if the bond is broken. Living organisms break these bonds under controlled conditions, which allow them to harness the energy of the bonds and use if for doing work (moving objects over distance).

The energy form most efficiently used by cells of living organisms is that contained in the bonds joining phosphate residues to certain organic compounds in the form of ATP, adenosine diphosphate (ADP), or creatine phosphate (CP) (Fig. 23-11). The energy ingested by organisms is often in the form of fatty acids, proteins, and carbohydrates. The energy in these ingested compounds is in the form of nonphosphate bonds, not in the form of ATP. To convert the energy from the ingested form (nonphosphate bonds) to the usable form (phosphate bonds of ATP), the following cascade of enzyme-mediated reactions is employed: (1) Glucose, amino acids, and fatty acids are converted to acetyl CoA (glycolysis converts glucose to acetyl CoA via pyruvate as an intermediary; diverse processes convert amino acids to acetyl CoA; beta oxidation converts fatty acid to acetyl CoA). (2) The Kreb cycle allows acetyl CoA to donate the electron-containing hydrogen ions needed to convert FAD to $FADH_2$ and convert NAD to NADH + $H^+$. (3) A subsequent enzyme-mediated transfer of electrons from $FADH_2$ and NADH + $H^+$ to oxygen creates a high concentration of electrons within the intermembrane space of the mitochondria. (4) The electron gradient between the mitochondria's intermembrane space and the mitochondria's cytosol then drives the formation of ATP from ADP and inorganic phosphate.[13]

Under normal circumstances, 60 to 80 percent of the ATP used by the heart is generated from fatty acids; the

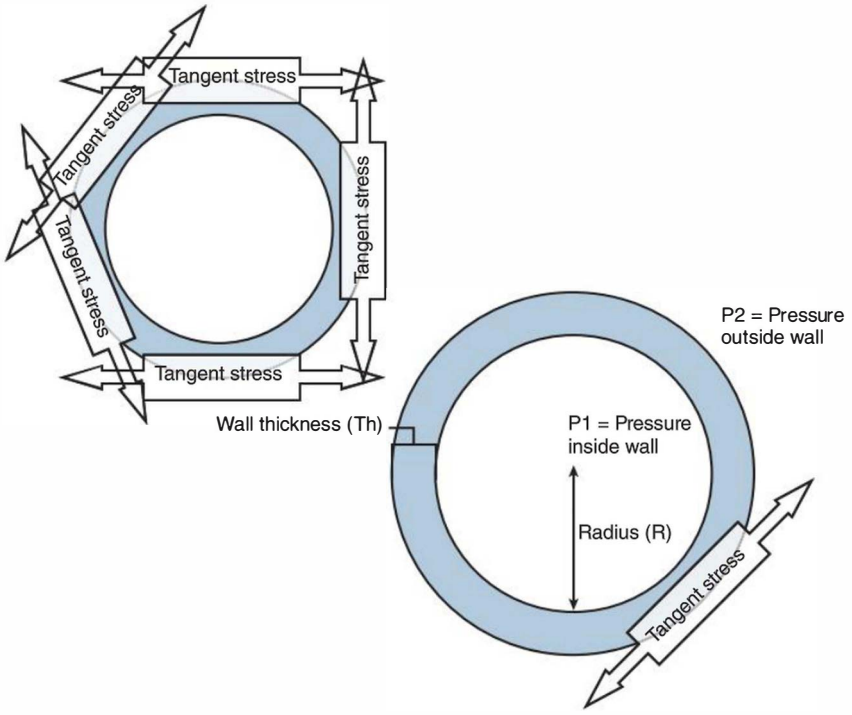



**FIGURE 23-10** Top left: Depiction of circle comprising multiple lines tangential to the radius of the circle. Bottom right: Tangential stress (T) = Pressure gradient across wall (P) × Radius of circle (R)/2 × Thickness of wall (Th), where P = P2 – P1.

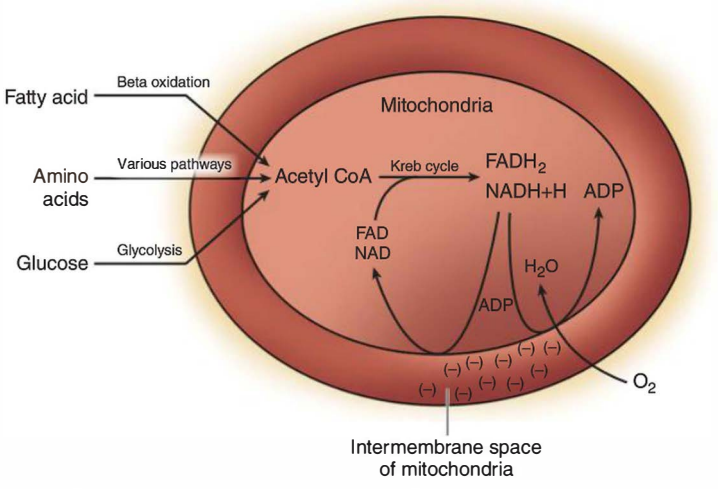



**FIGURE 23-11** Step 1: Conversion of fatty acid, proteins, a nd glucose to acetyl CoA. Step 2: Kreb cycle for production of electron donors. Step 3: Creation of electron gradient within mitochondrial intermembrane space. S tep 4: Utilization of electron gradient and oxygen to create ATP and water.

remainder is generated predominantly from glucose. Fatty acid oxidation produces more ATP than does glucose oxidation, but does so at the expense of less-efficient utilization of oxygen. Fatty acids are, however, maintained as the heart's primary energy source during ischemia because of modifications to fatty acid metabolism during ischemia. Nevertheless, the lack of oxygen reduces the cellular capacity to bind phosphate to ADP. Phosphate residues are sequentially removed from ADP, degrading it first to AMP and then to adenosine. The adenosine exits the myocyte to stimulate adenosine receptors, causing pain (angina).

As an alternative to oxidative phosphorylation, the body can also restore ATP levels by transferring a phosphate moiety from phosphocreatine (PC) to ADP. This phosphate transfer is used by the heart, skeletal muscle, and brain [the three organs containing the enzyme creatinine phosphokinase (CPK) under conditions of inadequate perfusion]. The PC is formed by the transfer of phosphate from ATP to creatine, a transfer occurring most readily under conditions of adequate tissue perfusion.

# CORONARY BLOOD FLOW

## Normal Coronary Blood Flow

Coronary blood flow supplies 60 to 90 mL/min of blood per 100 g of resting myocardium. The energy driving this perfusion is the pressure gradient between the proximal aorta (the origin of the coronary arteries) and the intraventricular pressure.[14] The influence of the intraventricular pressure derives from the fact that the same wall stresses responsible for generating intraventricular pressure also act to both decrease the pressure gradient driving the blood through the coronaries and compress the coronary vessels traveling through the myocardial wall. Because the gradient between intra-aortic pressure and intraventricular pressure is greatest when the ventricle is not contracting, the majority of coronary blood flow occurs during ventricular diastole. Coronary blood flow is both autoregulated and influenced by changing energy demands of the myocardial tissue. The factors affecting flow during periods of increased metabolic demand likely include neurohumoral factors as well as the factors responsible for autoregulation.

## Autoregulatory Mechanisms of Coronary Blood Flow

Factors intrinsic to the heart and its vasculature adjust the tone of coronary vessels smaller than 100 to 150 μm in diameter to assure that flow to the heart is kept constant in spite of changes in perfusion pressure to the heart. The mechanism includes a mixture of metabolic products, myogenic factors, and extrinsic compression by surrounding tissue.[14]

Metabolic products incriminated in coronary autoregulation include adenosine, prostaglandin, oxygen, carbon monoxide, carbon dioxide, and potassium concentrations in the tissue. Adenosine is an obvious candidate because, as stated earlier, it is produced in the heart at higher amounts during hypoxia. But removal of adenosine from interstitial spaces does not prevent coronary autoregulation, leaving other candidates as contributors. Prostaglandins can also cause dilation through stimulation of G protein-coupled receptors. This influence may be more pronounced when nitric oxide is less abundant, as in severe atherosclerotic disease. Hypoxia of the circulating blood or surrounding tissue may play a direct role by stimulating the opening of vascular smooth muscle cell K channels, which are coupled to the hypoxia sensitive cytochrome $b_{558}$. Similarly, low ATP levels can stimulate the opening of ATP-sensitive K channels in smooth muscle cells, causing vascular dilation. Nitric oxide dilates coronary vasculature through the activation of soluble guanylate cyclase. The release of nitric oxide is stimulated by hypoxia. Carbon monoxide can also activate soluble guanylate cyclase, making carbon monoxide (produced from the breakdown of heme to biliverdin) a possible mediator. Similarly, carbon dioxide has been shown to cause coronary dilation, possibly through a mechanism involving nitric oxide and/or cyclic guanosine monophosphate (GMP).

Myogenic contribution to autoregulation is the ability of smooth muscle cells to "sense" flow and alter tone to maintain flow constant. Mechanisms by which smooth muscle cells accomplish this are both unclear and difficult to evaluate in vitro. The majority of this response seems to occur in vessels between 30 and 70 μm in diameter. The cascade probably involves the sensing of altered intraluminal pressure or shear stress, the activation of nonspecific ion channels in the smooth muscle cell, and the phosphorylation of myosin light chains in the smooth muscle cell by myosin light chain kinase.

External compression of the coronary microvasculature by contraction of the surrounding tissue can also act as a feedback control of coronary blood flow. As coronary blood flow becomes inadequate, the force of myocyte contraction decreases due to limited energy supplies. This decreases the magnitude of the external forces acting to compress small coronary microvasculature, facilitating coronary blood flow.

## Physiologic Consequences of Coronary Insufficiency

### MYOCARDIAL ISCHEMIA

Myocardial ischemia is the condition whereby the myocardial blood flow and/or oxygen supply is insufficient to satisfy the demands of the myocardial tissue. This can reflect either an inappropriate limitation to blood flow (i.e., low-flow ischemia), an inappropriate excess in myocardial demand (i.e., high-flow ischemia), or low blood oxygen content such that oxygen delivery is insufficient in spite of appropriate blood volume supply and tissue demand (i.e., hypoxia or anemia). Myocytes respond by shifting their energy metabolism from

aerobic (mitochondrial) to anaerobic (glycolytic) pathways. Alternative sources of stored energy (other than ATP) are used, such as CP. These stores, however, are quite limited. As a result, metabolites of the complete breakdown of ATP (e.g., adenosine), metabolites of glycolysis (e.g., lactate), and a host of other substances (e.g., bradykinin, angiotensin) are released into the interstitial fluid.

During myocardial ischemia, energy reserves begin to decrease. This can result in dysfunction of any of the myocyte's energy-dependent diastolic function, systolic function, automaticity, and/or intercellular communication. Diastole, driven by ATP-dependent calcium uptake by the SR, is more sensitive to limited energy supplies than is systole. Diastolic dysfunction hinders relaxation, making it more difficult to fill the ventricle with blood. This lack of ventricular filling impairs the Frank–Starling mechanism, and thus limits the ability to compensate for systolic dysfunction. With more dramatic imbalances between myocardial oxygen supply and demand, all contractile capacity of the ventricle is lost. Whether this loss of contractile function is temporary or permanent depends in part upon the severity and duration of the energy supply–demand mismatch. Finally, insufficient energy impairs maintenance of membrane potentials by the nodal cells. This compromises the normal development of automaticity by SA node cells as well as conduction through AV node and Purkinje cells.

## MYOCARDIAL INFARCTION

An insufficient myocardial oxygen supply, if maintained too long, results in the utilization of all energy reserves by the myocardium. This leads to irreversible myocyte damage and begins to be seen after 20 min to 2 h of ischemia. With no energy, even the basic requirements for cell survival (i.e., exclusive of contractile function) cannot be maintained. Transmembrane ion concentrations are lost, and osmotic forces cause cell expansion to the point of membrane disruption and lysis of intracellular organelles. The tight junctions of intercalated disks between cells are disrupted, and cell-to-cell communication is lost. Recovery cannot occur following such catastrophic changes.

## "STUNNED" MYOCARDIUM

Reperfusion of ischemic myocardium does not always result in the return of normal myocyte function.[15,16] Dysfunction of reperfused tissue can persist in spite of blood and energy delivery capable of supporting much greater energy expenditure by the myocytes. The dysfunction that persists under these conditions is termed "stunning," an important characteristic of which is that it persists in the setting of a relative abundance of energy delivery. Other characteristics include the retained capacity of stunned myocardium to increase the force of contraction on exposure to inotropes as well as the lack of influence of β-agonists or β-blockers on the rate of recovery of stunned myocardium. The duration of stunning depends on factors such as the severity and duration of ischemia as well as the adequacy and immediacy of return of normal blood flow.

The cascade responsible for stunning is incompletely understood. Still, it is felt to involve oxygen-derived free radicals released during the early moments of reperfusion. Furthermore, it can be attenuated by using iron chelators such as deferoxamine. This suggests that hydroxyl radicals, generated from superoxide by an iron-catalyzed reaction, mediate at least part of the reaction. There is speculation that nitric oxide released during reperfusion may contribute through the formation of peroxynitrite after binding with the superoxide radicals. Unfortunately, free-radical scavengers have thus far been only inconsistently beneficial in preventing myocardial stunning. In any case, altered availability of calcium or sensitivity of myocyte myofibrils to calcium is chief suspect as to the mechanism by which contractile function is impaired.

## "HIBERNATING" MYOCARDIUM

Myocardial hibernation is another state of reversible myocyte dysfunction related to an insufficient blood supply.[17] In contrast to myocardial stunning, which occurs after formerly ischemic tissue has been reperfused with abundant blood supply, myocardial hibernation occurs while impaired blood delivery is ongoing. Thus, it is felt to be a way by which the myocyte preserves itself through decreasing energy expenditures to meet the energy supply available. The mechanism of myocardial hibernation is also unclear. Light-microscopically, there is a decrease in contractile elements, an increase in glycogen accumulation, and an alteration in the morphology of both the mitochondria and the T tubules. These changes are reversible, and contractile function is restored with the return of a normal blood supply. Positron emission tomography scanning, which utilizes labeled indicators of perfusion ($^{13}NH_3$) and of metabolism ($^{18}$FDG), remains the gold standard for distinguishing poorly contracting myocardium as potentially viable (hibernating).

## CORONARY ENDOTHELIAL FUNCTION

Rather than serving as a passive lining between the blood and vascular smooth muscle, coronary endothelial cells play an active role in preventing the development of myocardial ischemia.[18] Thus, the endothelium promotes anticoagulation, fibrinolysis, and vasodilation. It produces nitric oxide, which inhibits inflammation, platelet aggregation, leukocyte adhesion, and smooth muscle cell proliferation. It also provides vasodilatory and antioxidant effects.

The anticoagulation role of the endothelium evolves from the fact that the endothelium covers tissue factor (preventing contact between circulating factor VII and tissue factor) and is itself covered by antithrombin, protein C, protein S, and tissue plasminogen activator. When the endothelium is disrupted, then, circulating factor VII binds with the now-exposed tissue factor. This converts factor VII to its active form, and initiates the formation of thrombin. Thrombin

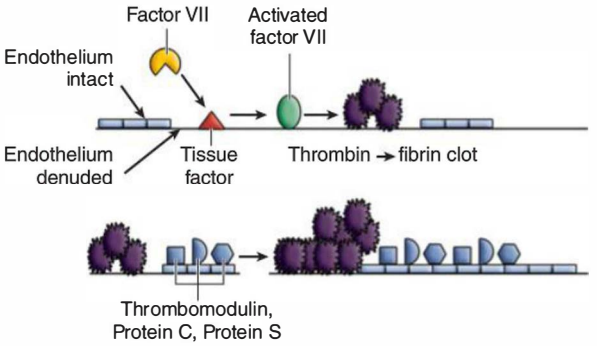



**FIGURE 23-12** Top: Disruption of endothelium exposes tissue factor to circulating factor VII. Tissue factor activates factor VII, initiating a cascade that ultimately results in production of fibrin clot. Bottom: As thrombin encounters thrombomodulin on surface of intact endothelium, the interaction allows for activation of protein C and protein S. This reverses prothrombotic reactions and leads to inhibition of clot progression.

converts fibrinogen to a fibrin clot. This cascade continues until thrombin contacts healthy endothelium. Exposure of thrombin to thrombomodulin on the healthy endothelial surface leads to the activation of protein C and protein S. Activation of these proteins *in*activates factors V and VIII. Because the activity of factors V and VIII expedite the production of thrombin, inactivation of these factors greatly reduces the prothrombotic cascade. Finally, tissue plasminogen activator, a serine protease released by the endothelium, is responsible for the conversion of inactive plasminogen to plasmin, which mediates fibrinolysis (Fig. 23-12).

This cascade highlights two concepts: (1) protein C and protein S are important in limiting clot propagation. They are vitamin K-dependent anticoagulant proteins, which can be more sensitive to Coumadin than is the production of many vitamin K-dependent procoagulant factors. The initiation of Coumadin therapy can therefore cause hypercoaguability prior to resulting in an anticoagulated state. (2) Although this antithrombotic cascade shows redundancy, optimal function requires the presence of all components. The opportunity for any single deficiency explains the relative abundance of hypercoaguable (vs hypocoaguable) conditions in the general population.

The vasodilatory effects of nitric oxide result from its stimulation of soluble guanylate cyclase, leading to a decrease in intracellular calcium. Nitric oxide's anti-inflammatory effect results principally from its ability to inhibit nuclear factor K-B, a transcription factor important in the regulation of many inflammatory proteins. It inhibits platelet aggregation by decreasing intraplatelet concentrations of calcium through a cascade similar to that by which nitric oxide causes vasodilation. It reduces leukocyte adhesion by decreasing the expression of vascular cell adhesion molecule via inhibition of nuclear factor K-B. Nitric oxide's capacity to inhibit smooth muscle cell proliferation is poorly understood but may involve its activation of PKA. The effect of nitric oxide on free radical balance is complex, although it is a potent inhibitor of free fatty acid, phosphatidylcholine, and low-density lipoprotein (LDL) oxidation.

Nitric oxide can be stimulated by neurohumoral mediators (e.g., acetylcholine), by products released by circulating cells (e.g., bradykinin, serotonin), or by mechanical forces (e.g., shear stress). Nitric oxide production is impaired by atherosclerosis through a series of mechanisms. First, atherosclerotic plaques physically exclude endothelial cells from the stimulants for its release (e.g., shear stress). Second, there is a direct effect of cholesterol components (e.g., lysophosphatidylcholine, a component of oxidized LDL) on the nitric oxide signaling pathway [i.e., protein kinase C, G proteins, and caveolin–endothelial nitric oxide synthase (eNOS) interaction]. Finally, cholesterol enhances the activity of the superoxide-producing reduced nicotinamide adenine dinucleotide phosphate oxidase and xanthine oxidase enzyme systems within the vascular wall. Since oxygen radicals scavenge nitric oxide, this effectively decreases the bioavailability of the decreased amounts of nitric oxide produced.

## PHYSIOLOGY OF HEART FAILURE

### Systolic Dysfunction

Heart failure is a syndrome of dyspnea, fatigue, and fluid retention that may result from the inability of the heart to fill with, and/or eject blood. It can be asymptomatic (stage A or stage B) or symptomatic (stage C or stage D). In stage A, the asymptomatic patient essentially has no heart failure but has medical risk factors that predispose to heart failure (coronary artery disease, hypertension, diabetes). In stage B, the asymptomatic patient has structural indications of impending heart failure (LV hypertrophy, impaired LV function). Stage C indicates current or past symptoms and stage D indicates refractory symptoms. These stages emphasize the progressive nature of this disease. This classification is meant to complement the New York Heart Association (NYHA) functional classification, which characterizes the functional limitations being experienced at a point in time by the patient with stage C or stage D disease. (Class I—symptoms only with severe exertion, Class II—symptoms with ordinary exertion, Class III—symptoms with less-than-ordinary exertion, Class IV—symptoms at rest.) Thus, though a patient may vary from NYHA classification III to NYHA classification I, they will not regress from stage C to stage A.

Systolic dysfunction is the impaired ability of the ventricle to generate force and shorten.[19] The symptoms depend on which ventricle fails. Left ventricular failure prohibits egress of blood from the pulmonary vasculature, leading to pulmonary symptoms of shortness of breath. Right ventricular failure prevents blood from exiting the systemic vasculature (viscera, lower extremities, head), leading to hepatic congestion, lower extremity edema, and distended jugular veins. The precipitating events can be ischemic, infectious, or idiopathic. Although infiltrative (e.g., amyloidosis) processes

may cause systolic dysfunction, these usually lead primarily to diastolic dysfunction. Prognosis is worse when the etiology is ischemic rather than nonischemic in origin.

In patients without heart failure symptoms (stage A or stage B), reduction in risk factors (hypertension, diabetes, elevated cholesterol) is recommended. β-Blockers are suggested if history of myocardial infarction, and coronary revascularization if ACC/AHA Guidelines indicate. In patients with symptoms (stage C or stage D) from systolic dysfunction, aseries of randomized placebo-controlled studies have documented the beneficial effects of various medication classes on progression and mortality. β-Blockers, likely due (at least in part) to their inhibition of the adrenergic pathway, improve both clinical status and overall mortality. Angiotensin-converting enzyme (ACE) inhibitors, likely due to their effect on the renin–angiotensin–aldosterone system, show benefits similar to those of beta blockade. The effects of ACE inhibitors may be additive to those of β-blockers. There is growing evidence that angiotensin-receptor antagonists demonstrate benefits similar to those of ACE inhibitors, also likely through inhibition of the renin–angiotensin–aldosterone system. The effects of this class of medications may be additive to those of both β-blockers and ACE inhibitors. Although growing evidence as well as our current understanding of the pathophysiology of systolic dysfunction suggests that the role of angiotensin II receptor blockers will be similar to that of ACE inhibitors in the therapy of systolic dysfunction, they are currently not recommended as an alternative to ACE inhibitors except in those patients who cannot tolerate the latter. Similarly, although hydralazine with a nitrate may help to reduce the progression of abnormal myocardial/vascular growth, there is currently not enough evidence to recommend this combination as an alternative to ACE inhibitors except in those patients who cannot tolerate the latter. Digoxin has been shown to improve symptoms, but it does not alter mortality. Calcium channel blockers may actually worsen mortality in patient with compromised LV systolic function, if the history of cardiac arrest, ventricular fibrillation, or hemodynamically destabilizing tachycardia, an implantable cardioverter-defibrillator (ICD) is recommended to prolong survival. In those with ischemic heart disease, an ICD is also recommended if LV ejection fraction (LVEF) ≤30 percent in patient with at least 40 days post-myocardial infarction and life expectancy >1 year. If nonischemic heart disease, an ICD is recommended if NYHA functional class II or III symptoms on optimal medical therapy and life expectancy >1 year. In those with cardiac dyssynchrony (QRS >0.12 ms) and NYHA functional class III or IV with LVEF ≤35 percent, cardiac resynchronization is recommended if no contraindications exist.

## Diastolic Dysfunction

Diastolic dysfunction is the inability of the myocardium to stop generating force, to shorten, and/or to completely return to its unstressed force and length in the normal time period.[20,21] Though it can occur in combination with systolic dysfunction, diastolic dysfunction may be the sole cause of dysfunction in up to 50 percent of heart failure patients. As there is no consensus definition of what normal diastolic function is, the diagnosis of isolated diastolic dysfunction requires verification of the presence of heart failure, the absence of systolic dysfunction, and the exclusion of other processes (e.g., anemia, pulmonary dysfunction, hypothyroidism) that can masquerade as heart failure.

Isolated diastolic heart failure appears more frequently in older (vs younger), hypertensive (particularly isolated systolic hypertension), and female patients. It mimics systolic dysfunction in symptoms, hospitalizations, and mortality. The mechanism leading to its development is unclear, although increasing interest is being directed at the role of aldosterone. Aldosterone also acts via mineralocorticoid receptors to stimulate deposition of collagen and extracellular matrix. The RALES (Randomized ALdactone Evaluation Study) trial showed that the aldosterone inhibitor spironolactone, at doses devoid of blood pressure effects and having little or no effect on LV mass, prevents cardiac collagen accumulation in renovascular hypertension with high aldosterone levels. There are no randomized double-blind prospective studies demonstrating that a specific drug can reduce mortality or morbidity in patients with diastolic heart failure. The role of beta blockade has been debated. Although myocardial relaxation is more energy-dependent than is contraction, canine studies suggest that early diastolic relaxation is impaired by β-adrenergic inhibition. Furthermore, a lack of reduction of episodes of pulmonary edema following coronary revascularization in patients with isolated diastolic dysfunction suggests that ischemia does not play a predominant role. Still, the general long-term benefits of beta blockade combined with its ability to reverse LV hypertrophy make it difficult to exclude. The perindopril in elderly people with congestive heart failure (PEP-CHF) and candesartan in heart failure assessment of reduction in mortality and morbidity (CHARM)-preserved studies failed to demonstrate a reduction in death (all-cause death in PEP-CHF and cardiovascular death in CHARM-preserved) by using the ACE-inhibitor perindopril or the angiotensin receptor blocker candesartan, respectively. Still, these studies each suffer major weaknesses. In PEP-CHF, many patients withdrew and started taking open-label ACE inhibitors. In CHARM-preserved studies, many of the patients did not show echocardiographic signs of diastolic dysfunction. These study limitations, combined with the theoretical role of the renin–angiotensin–aldosterone pathway, suggest that ACE inhibitors, angiotensin II receptor blockers, and a reduction in aldosterone, have sustained hope that interrupting this axis may reduce morbidity in diastolic heart failure. The results of two large-scale, randomized studies (I-PRESERVE comparing irbesartan to placebo, and TOPCAT comparing spironolactone to placebo) are expected soon. There are not consistent data to suggest that calcium channel blockade, particularly using dihydropyridine calcium channel antagonists, are effective in reversing this process.

## Adaptive Changes in Chronic Congestive Heart Failure

Chronic heart failure results in myocardial adaptations teleologically consistent with optimizing distribution of wall stress as explained by Laplace's law. Thus, when pressure overload increases wall stress, the myocyte wall thickens through parallel hypertrophy to reduce the tension sensed by each myocyte back down to normal levels. By contrast, the myocyte's replication is predominantly serial, with only mild parallel replication when volume overload is the predominant stimulus.

The pathways leading to these changes seem to involve a number of mediators. There is reexpression of fetal proteins which, although increase myocyte mass, contract less effectively than their adult counterparts. There is an increase in collagen and fibrous tissue deposition, both interstitial and perivascular. This may decrease diastolic compliance and limit dilatory reserve of the coronaries. There is a paucity of mitochondrial and vascular growth relative to myocyte replication, decreasing the vascularity and energy available relative to the number of myocytes. Calcium handling deteriorates, due to a relative decrease both in the amount of SR and in the function of the calcium pumps on the SR. Finally, the composition of the myosin light chains in the ventricular sarcomeres changes. This decreases the effectiveness of the actin–myosin unit and possibly its sensitivity to calcium. As stated earlier, the cascades leading to this remodeling appear to involve the adrenergic system, the renin–angiotensin–aldosterone system, neurohumoral pathways, and dysfunction of the endothelial system. This understanding has led to our current therapy profile to prevent the progression of remodeling from beneficial to maladaptive. In addition, there is anecdotal evidence suggesting that mechanical unloading of decompensated hearts may lead to a regression of the maladaptive changes by a yet unclear mechanism.

## Cardiac Chamber Remodeling after Surgical Correction

### CORONARY ARTERY BYPASS GRAFTING

Revascularization is felt to improve regional and global ventricular function in addition to reducing infarct size.[22] Thus, complete revascularization of patients with recent heart failure, LVEF below 40 percent, and large areas of myocardium at risk (as evidenced by thallium imaging or nitrate-enhanced 99m-technetium sestamibi) increases LVEF and decreases LV end-systolic volume. This correlates with a significant trend toward improved 40-month survival. Though unproven, it is hypothesized that the salutary effect of revascularization on remodeling derives from reducing wall stress by recapturing maximal function in previously hibernating and stunned myocardium. Furthermore, vascular stenosis leads to thickening and perivascular fibrosis of arteries and small vessels distal to the stenosis. This may limit the vasodilatory reserve of these vessels, compounding the ischemia associated with vascular remodeling.

### AORTIC VALVE REPLACEMENT

***Aortic Stenosis.*** Aortic stenosis leads to systolic and/or diastolic LV dysfunction. Aortic valve replacement (AVR) is currently recommended for patients with symptomatic aortic stenosis and hemodynamic evidence that their aortic stenosis is severe (i.e., with an aortic valve area $<0.9$ cm$^2$). If asymptomatic, it is recommended for those patients who have a hypotensive response to exercise, evidence of progressive LV dysfunction, or who are undergoing another cardiovascular surgery.

Cardiac remodeling after AVR is quite dramatic when it is performed to relieve aortic stenosis.[23] Complete recovery of both systolic and diastolic function is possible. Recovery of systolic function usually precedes recovery of diastolic function. Recovery is more likely, and operative mortality is lower, if preoperative impairment is less severe (i.e., not NYHA class III or IV). Still, the poor prognosis with medical treatment alone often makes AVR the most advisable option in NYHA class III and IV aortic stenosis patients. The elevated LV mass characteristic of severe aortic stenosis is reduced 18 months following AVR and almost completely resolved by 5 years following AVR. Regression may be more rapid when stentless aortic valves are used. It is hypothesized that patients with aortic stenosis who have the deletion/deletion polymorphism for the ACE gene are more predisposed to left ventricular hypertrophy (LVH), and more likely to have LVH regress following AVR.

***Aortic Insufficiency.*** Surgical repair of aortic valvular insufficiency is indicated in symptomatic patients and in asymptomatic patients with evidence of progressive deterioration of LV function (LVEF <50 percent or LV end-diastolic diameter >5.5 cm).

Like AVR for stenotic disease, AVR for insufficiency results in a regression of the adaptive changes precipitated by the insufficiency.[24,25] Thus, myocardial hypertrophy is regresses toward normal at 1.6 years following surgery and is often normal by 8.1 years. Regression is delayed and less complete in patients with severe preoperative dysfunction (NYHA classification III or IV or LV ejection fraction below 25 percent).

### MITRAL VALVE REPLACEMENT AND REPAIR

***Mitral Stenosis.*** Mitral valve surgery for mitral stenosis involves either dilation (i.e., commissurotomy), repair (i.e., reconstruction), or replacement. The relative benefits of mitral commissurotomy versus replacement (MVR) vary among investigators.[26–28] Universally, however, commissurotomy is associated with a higher likelihood of traumatic insufficiency as well as higher reoperation rates (due to insufficiency and/or restenosis). In contrast, commis-

surotomy can often be performed with equal success using transvenous or open procedures, dramatically reducing early postprocedure morbidity and recovery time. This makes transvenous commissurotomy an attractive alternative for the older patient with limited life expectancy.

The benefit of MVR for mitral stenosis is inconsistent, possibly reflecting the varied pathology and progression of rheumatic mitral valve stenosis. In addition, the maintenance of an intact subvalvular apparatus (i.e., mitral ring, chordae, and papillary muscles) is both possible and important in MVR surgery. This apparatus can be responsible for 25 percent of LV contractile function.

***Mitral Insufficiency.*** Mitral valve surgery for insufficiency can involve either repair (e.g., reconstructive) or replacement. Options for repair include annuloplasty, resection of the prolapsing segment(s), and repair (i.e., shortening, elongating, reimplanting, replacing) of dysfunctional chordae tendineae or papillary muscle(s). Surgical repair is more likely to be successful when patients are younger (more pliable valves), the procedure requires chordal/papillary muscle shortening (rather than lengthening), and the etiology is endocarditis or ischemia (vs rheumatic heart disease).

The increasing interest in mitral valve repair rather than replacement surgery stems from dissatisfaction with the effects of replacement surgery upon LV function.[29] LV contractile function, as depicted by LVEF, is depressed following MVR for mitral insufficiency. This was initially felt to represent an unmasking, by the removal of the low pressure "pop-off" of regurgitant flow into the low-pressure left atrium, of preexisting LV dysfunction. It is more recently appreciated, however, that the subvalvular apparatus (i.e., annulus, chordae, and papillary muscle structure) helps prepare the LV for normal contraction and accounts for up to 25 percent of the LV systolic function. Conservation of an intact subvalvular apparatus is therefore a priority in mitral valve surgery.

Unlike remodeling following AVR for aortic stenosis, the LV typically does not improve its contractile function following MVR for mitral insufficiency. Although the majority of patients improve symptomatically, their left ventricular ejection fraction often deteriorates. Preoperative predictors of poor outcomes include NYHA classification III or IV, age above 60 years, end-systolic left ventricular diameter greater than 5.2 cm, and LVEF less than 50 percent. For patients below age 60 in NYHA classification I or II, with end-systolic left ventricular diameter less than 4.5 cm and LVEF greater than 60 percent, functional survival is excellent.

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## CARDIOVASCULAR FUNCTION AND PHYSIOLOGY BOARD REVIEW QUESTIONS (CHAPTER 23)

1. Which of the following is correct regarding hibernating myocardium?
   A. Does not contract despite adequate energy supply
   B. Decreases force of contraction as a response to inadequate energy supply
   C. Continues to contract poorly after return of adequate energy supply
   D. Actively stores energy because immediate demands are low
   E. Has discontinued all metabolic activity due to complete absence of energy supply

2. Which is true regarding function of the endothelium?
   A. Stores protein C and presents tissue factor to circulating blood
   B. Prevents exposure to thrombomodulin
   C. Limits initiation of clots by covering tissue factor
   D. Blocks release of nitric oxide from underlying smooth muscle cells
   E. Provides fertile surface for initiation of thrombus

3. Which of the following influences speed of myocardial contraction?
   A. Resting length of the myocyte
   B. Sudden stretch of the myocyte
   C. Rapid repeated contraction of the myocyte
   D. All of the above
   E. None of the above

4. Which is correct regarding cardiac remodeling after surgery?
   A. Aortic stenosis: begins with systolic recovery and is complete by 18 months.
   B. Ischemic heart disease: demonstrates an increase in LVEF and a decrease in left ventricular end-diastolic volume (LVEDV) with complete revascularization.
   C. Aortic insufficiency: rapid recovery complete by 6 months.
   D. Mitral stenosis: recovery easily predicted by preoperative TEE.
   E. Mitral insufficiency: sustainable recovery is unlikely in young patients.

5. Which is true for myocardial function?
   A. The primary energy source for the myocardium is glucose.
   B. Diastole is more energy dependent than systole.
   C. LV hypertrophy compromises endothelial perfusion on the sole basis of increasing distance of capillary blood flow.
   D. Increased wall thickness increases wall stress.
   E. The uniform distribution of ion channels throughout the heart stabilizes electrical activity.

## ANSWERS

1. **Answer: B.** Hibernating myocardium decreases force of contraction when there is inadequate energy supply. It will contract normally when there is adequate energy supply but does not actively store energy. The energy supply is enough to provide basic metabolic needs.
2. **Answer: C.** Endothelium limits the initiation of clots by covering tissue factor, which prevents activation of circulating factor VII. This layer contains thrombomodulin, which also limits clots, and produces nitric oxide. The endothelium is therefore not a fertile surface for thrombus.
3. **Answer: E.** Speed of myocardial shortening is determined by afterload. Strength of contraction, however, is influenced by all of the above factors.
4. **Answer: B.** After revascularization, myocardial recovery is seen as an increase in LVEF and a decrease in LVEDV. Recovery after AVR for aortic stenosis may not be complete for up to 5 years. Remodeling after AVR for aortic insufficiency may be even further delayed for up to 8 years. Operations for mitral stenosis are varied and prediction of recovery after surgery is inconsistent. Mitral valve repair is most likely to be successful and durable in young patients.
5. **Answer: B.** Diastole is more energy-dependent, and ischemia may therefore present as diastolic dysfunction before systolic dysfunction occurs. The primary energy source for the myocardium is fatty acids. There are at least three mechanisms that compromise LV myocardial perfusion, including distance of blood flow across the thickened wall, elevated LVEDP, and compression of myocardial vessels. Increased wall thickness decreases wall stress. Ion channels are not uniformly distributed throughout the heart.

# 24 Cardiopulmonary Bypass

*Edward H. Kincaid*
*John W. Hammon*

Cardiopulmonary bypass (CPB) has developed into an invaluable tool for operations on the thoracic viscera. By interfacing with the cardiovascular system, total CPB completely replaces the function of the heart and lungs for a short time. Modifications of CPB have been designed to partially replace or control more specific aspects of the cardiopulmonary systems. To fully utilize the tremendous flexibility available with "the pump," one must understand its components, operation, and potential for complications.

## HISTORY

The development of CPB is a testament to personal perseverance and collaboration and demonstrates how cardiac surgery has truly evolved as a science. Initial progress in the field of extracorporeal circulation required mastery of the principles of total-body oxygen delivery and consumption. Later, further refinements in the understanding of metabolic demands at the cellular level served to enhance the safety and flexibility of circulatory support. Undoubtedly the most important milestone in the development of CPB is John Gibbon's use of the first clinical application of CPB. In 1953, after devoting most of his career to this work, he successfully repaired an atrial septal defect in a young woman with a pump-oxygenator. Additional milestones include the work of Bigelow, who, in the early 1950s, reported on systemic hypothermia with topical cooling as a means to reduce oxygen demand during the periods of reduced oxygen delivery inevitably encountered during operations on the heart. Shortly thereafter, Lillehei began performing congenital repairs using "cross circulation," employing a parent's cardiopulmonary system to support a child's during cardiac surgery. Finally, in the mid-1950s, Kirklin and colleagues at the Mayo Clinic ushered in the era of routine congenital repairs using the Mayo–Gibbon pump-oxygenator. Modern refinements in equipment and techniques have subsequently evolved as a consequence of the proliferation of coronary revascularization surgery and increased industrial interest.

## COMPONENTS OF THE CPB CIRCUIT

Current-generation CPB circuits maintain much of the simplicity of older perfusion equipment but have much more flexibility and ability to more precisely control various perfusion parameters. Core components of any circuit include cannulas, tubing, a pump, and an oxygenator (Fig. 24-1). In reality, however, even basic circuits used in routine clinical practice include many other features such as additional pump heads for suction, venting of the heart, and delivery of cardioplegia. Venous reservoirs are also needed to maintain adequate circuit volume and remove air. Filters are required at various levels to prevent embolic complications. Finally, a heat exchanger facilitates systemic and myocardial cooling and rewarming.

## CANNULAS

### Arterial Cannulation

Cannulation for CBP is typically performed centrally with an inflow cannula in the ascending aorta and outflow cannula(s) in the right atrium. Basic requirements for an arterial cannula include a size large enough to permit adequate flows without creating excessive back pressure at the pump head. At the same time, the size and design of the cannula must allow for easy placement with minimal vessel trauma. Beyond these basic requirements, a multitude of other aspects of cannula design may arguably affect performance. Such features include tip angle, size and number of end or side holes, wire reinforcement, and filters. Most arterial catheters are rated by a performance index, which relates external diameter, flow, and pressure differential. High-velocity jets may damage the aortic wall, dislodge atheroemboli, produce dissections, disturb flow to nearby vessels, and cause cavitation and hemolysis. Aortic catheters with only side ports are designed to minimize jet effects and better distribute arch vessel perfusion and pressure; they may be associated with fewer strokes.[1]

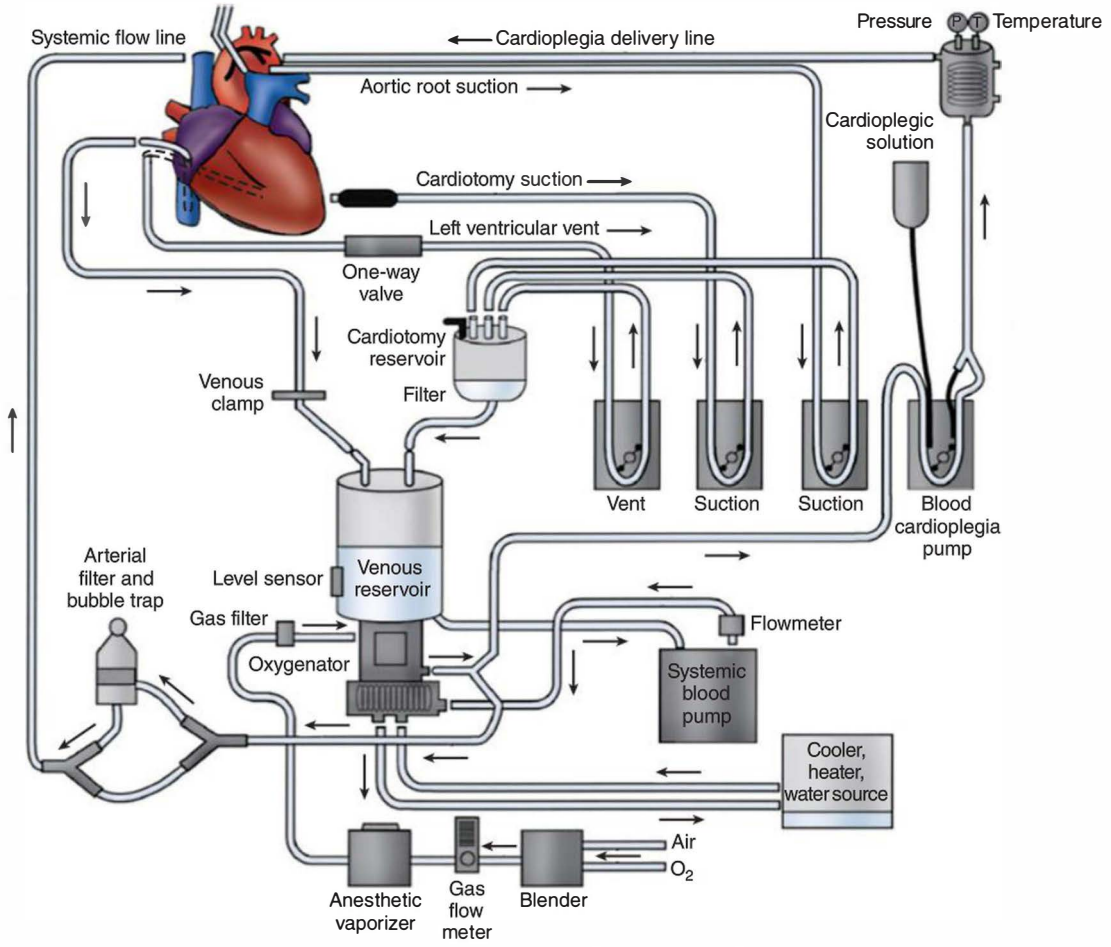



**FIGURE 24-1** Schematic of typical CPB circuit. (Reprinted with permission from Cohn LH, Edmunds LD Jr (eds). *Cardiac Surgery in the Adult*, 2nd ed. New York: McGraw-Hill, 2003.)

## AORTIC CANNULATION

Various locations on the ascending aorta and aortic arch are most often used as sites for insertion of the arterial cannula because of the simplicity and maintenance of antegrade blood flow. In patients with no significant ascending aortic atherosclerosis, this location is also associated with the least risk of inflow-related complications in routine cardiac cases. However, multiple other locations can be good alternatives, including the common femoral, axillary, and innominate arteries; descending thoracic aorta; and rarely the left ventricular (LV) apex. The choice is influenced by the planned operation and the distribution of atherosclerotic disease.

To cannulate the ascending aorta, most surgeons place two purse-string sutures with or without pledgets partially through the aortic wall to encompass a diameter of approximately 1 to 1.5 cm. Next, with a systolic blood pressure preferably less than 100 mm Hg, a 4- to 5-mm full-thickness stab wound is made, occasionally dilated, and then controlled under finger or forceps pressure. The cannula is then inserted under the finger or forceps approximately 1 to 2 cm into the lumen of the aorta. Backbleeding is detected to ensure that the tip is completely within the lumen and positioned to direct flow to the midtransverse aorta. A long catheter with the tip placed beyond the left subclavian artery may also be used. Proper cannula placement is critical and is confirmed by noting pulsatile pressure in the aortic line monitor and equivalent pressure in the radial artery.

Complications of ascending aortic cannulation include bleeding from tears in the aortic wall, malposition of the cannula tip, atheromatous or air emboli, and aortic dissection. It is essential to monitor aortic line and radial artery pressures and to carefully observe the aorta for possible cannula-related complications during the onset of CPB and placement of aortic clamps. Asymmetrical cooling of the face or neck may suggest a problem with cerebral perfusion. Late bleeding and infected or uninfected false aneurysms are delayed complications of aortic cannulation.

### FEMORAL ARTERY CANNULATION

The common femoral artery is probably the second most common location for CPB inflow. Reasons for cannulating the femoral artery include inadequacy or inavailability of the ascending aorta in cases such as aortic dissection, reoperation, descending aortic surgery, and minimally invasive cardiac procedures. Severe atherosclerosis of the ascending aorta is generally not a good indication for femoral cannulation because of the likely coexistence of severe disease in distal segments of the aorta and iliac arteries. Alternative strategies for CPB in this scenario are discussed later in this chapter.

Exposure of the femoral artery is through a small oblique incision just below the inguinal ligament. Only the anterior surface of the vessel needs to be exposed. After placement of a 5-0 monofilament purse-string suture, the common femoral artery is punctured and a guidewire is passed to the aorta. Transesophageal echocardiography (TEE) guidance can be used to confirm the location of the wire. A long, thin-walled cannula is then passed over the wire into the distal aorta. Most adult men can be perfused adequately with a 21F cannula; in women, a 19F cannula usually suffices.

Disadvantages of femoral cannulation include local complications such as vessel injury or groin wound complications and perfusion-related problems. These include abdominal aortic dissection or perforation, embolic phenomena from retrograde flow through a diseased abdominal aorta, and malperfusion of aortic branches in acute aortic dissection. In addition, ischemic complications of the distal leg may occur during prolonged retrograde perfusions; these may result in the release of myoglobin and subsequent renal injury. Finally, some speculate that retrograde flow to the cerebral and coronary arteries may result in lower perfusion pressures or oxygen saturation of blood at the end of the perfusion stream.

### OTHER SITES OF ARTERIAL CANNULATION

The axillary subclavian artery is increasingly used for cannulation.[2,3] Advantages include freedom from atherosclerosis, antegrade flow into the arch vessels, and protection of the arm and hand by collateral flow. Due to these advantages and the dangers of retrograde perfusion in patients with aortic dissection, some surgeons prefer this cannulation site for this and other conditions involving the aortic arch. The right axillary artery is usually used and is approached through a subclavicular incision, taking care not to damage the adjacent brachial plexus. In order to prevent injury to the fragile axillary or subclavian artery, some prefer to anastamose a small-caliber graft end to side to the axillary artery followed by insertion of the cannula into the graft.

## Venous Cannulation

In most applications, venous blood enters the circuit through negative pressure generated by siphonage. Thus, venous return flow rates are determined largely by the height differential between the right atrium and venous reservoir. Venous return can be impeded by resistance in cannulas, tubing, and connectors and may cease completely with entrainment of significant amounts of air into the venous line, creating an "air lock." This situation can be managed by correcting the source of air entrainment (e.g., tightening a loose purse-string suture) and then elevating the venous tubing such that the air rises in the direction of the venous reservoir. Continued arterial inflow from the pump creates positive central venous pressure, which will eventually drive the air into the reservoir, where it evacuates. Venous cannulas are usually made of flexible plastic, which may be stiffened against kinking by wire reinforcement. The size required is determined by the patient's size, the anticipated flow rate, and cannula flow characteristics, such as resistance. Catheters are typically inserted through purse-string–guarded incisions in the right atrial appendage, lateral atrial wall, or directly in the superior vena cava (SVC) and inferior vena cava (IVC).

Two basic approaches for central venous cannulation are used. For coronary artery or aortic valve operations, single venous cannulation of the right atrium alone suffices. In adults, this is usually performed with a 40F to 46F "two-stage" device that has a set of drainage holes in the distal portion and a second set located more proximally (Fig. 24-2). The distal end is positioned in the IVC while the proximal side holes drain the right atrium. This cannula may provide for better drainage than a single-stage cannula, especially when positioning of the heart may kink the venae cavae. Bicaval cannulation is used primarily for isolating the right atrium when surgery dictates opening this chamber. Caval tourniquets are also necessary in this situation to prevent bleeding and air entry into the system. Because of coronary sinus return, caval tourniquets should not be tightened without decompressing the right atrium. Bicaval cannulation is often preferred to facilitate venous return during exposure of the left atrium and mitral valve, mainly because of the potential

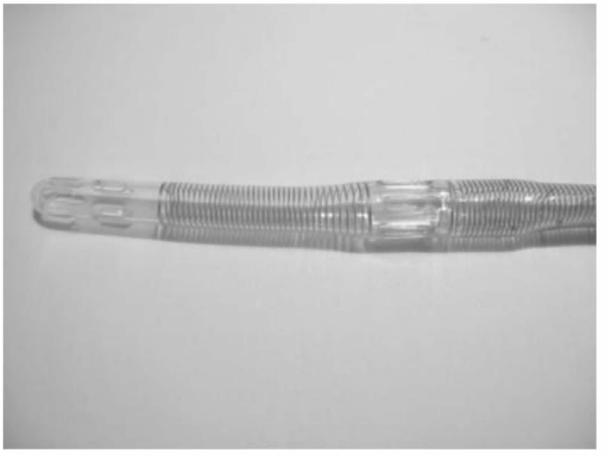


**FIGURE 24-2** Two-stage venous cannula with separate drainage holes for the inferior vena cava and right atrium.

for obstruction of the SVC or IVC during exposure. Using both techniques, the operative team should carefully monitor central venous pressure to prevent obstruction of the SVC.

Placement of a single venous cannula is most easily accomplished through the right atrial appendage. After application of a vascular clamp, the right atrial appendage is excised, or it may be opened longitudinally when the appendage is small. A purse-string suture is then placed just below the free edges, which are controlled with forceps. After release of the clamp, the cannula is inserted toward the IVC. The height of blood within the unclamped cannula is a good measure of central venous pressure. During bicaval cannulation, the IVC cannula is generally placed on the lateral wall of the right atrium near the junction with the IVC. During placement of the purse-string suture, the right atrium is gently retracted with the assistant's hand or forceps while monitoring hemodynamics. A stab incision is made in the middle of the purse-string, the defect is dilated with a curved clamp, and the cannula, either straight or right-angled, is then directed into the IVC. The cannula should not be inserted with the proximal side holes located too distally within the IVC, as this may impede hepatic venous drainage. SVC cannulation is typically accomplished with either a straight cannula placed through the lateral wall of the atrium, as in IVC cannulation, or with a right-angled cannula placed directly into the SVC. In this procedure, the anterior surface of the SVC is exposed by dividing the pericardial reflection overlying its superior border. An oval-monofilament purse-string suture oriented longitudinally is placed, and an incision is made along the length of the purse-string suture while controlling the free edges with forceps. The tip of the cannula is then directed superiorly, taking care to avoid tip placement in the azygos vein.

Access to the central venous system for blood return can also be obtained through the common femoral or internal jugular veins. Remote cannulation for CPB is particularly beneficial for reoperative cardiac procedures, minimally invasive "on-pump" cardiac procedures such as mitral valve repair via right thoracotomy/thoracoscopy, and aortic surgery through a left thoracotomy. Depending on the size of the cannula, either open or percutaneous methods can be used. Most surgeons would recommend a maximum size of 21F to 22F for percutaneous venous access without the need for direct vessel repair after decannulation. Typically, a long, wire-reinforced cannula with an ultrathin wall is advanced over a guidewire through the femoral vein to the right atrium under transesophageal TEE guidance. For bicaval drainage, some femoral venous cannulas are designed to be advanced into the SVC; multiple levels of side holes subsequently drain both venae cavae individually. An alternative strategy for bicaval drainage employs two individual venous cannulas, one in the femoral vein to drain the IVC and one in the right internal jugular vein to drain the SVC.

As an adjunct to remote cannulation for venous drainage, most surgeons employ some means of active assist over the standard gravity or siphonage power for blood return. "Assisted venous return" can be achieved by applying a regulated vacuum to a closed hard-shell venous reservoir or by kinetically assisting return via a centrifugal pump placed in the venous return line. Assisted venous return is also useful in cases using standard central cannulation sites but where the use of smaller cannulas may be beneficial, such as a MAZE procedure or operation through a ministernotormy. The most significant disadvantage of assisted venous drainage is an increased risk of air entrainment and subsequent microembolization to the arterial circulation.[4,5]

## TUBING AND CONNECTORS

The various components of the heart–lung machine are connected by polyvinyl tubing and fluted polycarbonate connectors. Medical-grade polyvinyl chloride tubing is universally used because it is flexible, compatible with blood, inert, smooth, transparent, resistant to kinking and collapse, and can be heat-sterilized. In adults, 1/2-in. tubing is generally used for inflow and 5/8-in. tubing for outflow. Wider tubing improves flow dynamics but also increases priming volume. Tubing lengths between patient and pump should also be minimized so as to reduce priming volume.

One controversy that continues over tubing is the use of herparin bonding to the interior surfaces, a technique that has many theoretical advantages associated with a reduced blood–plastic interface. The use of heparin-coated circuits during CPB has some proven advantages,[6–8] such as reduced activation of complement pathways. However, there is only weak evidence that heparin-coated perfusion circuits reduce the need for systemic heparin or reduce bleeding or thrombotic problems associated with CPB, and the overall inflammatory response to CPB is not reduced.

## PUMPS

Two types of pumps can be used, and each has its own set of advantages and disadvantages. Centrifugal pumps consist of a vaned impeller or of nested, smooth plastic cones, which, when rotated rapidly, propel blood by centrifugal force. An arterial flowmeter is required to determine forward blood flow, which varies with the speed of rotation and the afterload of the arterial line. Centrifugal pumps produce pulseless flow and generate less negative pressure; therefore, they may produce less cavitation and fewer gaseous microemboli. They can pump small amounts of air but become "deprimed" if more than 30 to 50 mL of air enters the blood chamber. Centrifugal pumps are probably superior to temporary extracorporeal assist devices and left-heart bypass, for assisting venous return. They are often used as the arterial inflow pump on the CPB circuit.

Roller pumps consist of two rollers situated 180 degrees apart inside a curved raceway. Forward flow is generated by roller compression of tubing, which can be sized from 1/4 to 5/8 in. ID depending on flow requirements. Flow rate depends on the diameter of the tubing, rate of rotation, length

of the compression raceway, and completeness of compression, which is adjusted to be barely nonocclusive against a standing column of fluid that produces 45 to 75 mm Hg of back pressure. At this degree of compression, hemolysis and tubing wear are minimal. Flow rate is determined from calibration curves for each pump for different tubing sizes and rates of rotation. Roller pumps are inexpensive, reliable, and safe; they are insensitive to afterload, have small priming volumes, but can produce high negative pressures and may shed microparticles from compressed tubing. Roller pumps are used almost exclusively for vents, sucker systems, and the delivery of cardioplegia.

One advantage roller pumps have is the ability to produce pulsatile blood flow. Normally, standard roller pumps produce a sine-wave pulse of around 5 mm Hg, but they can be set to generate pulse pressures above 20 mm Hg as detected on peripheral arterial pressure monitors. Theoretically, pulsatile perfusion delivers more energy to cells and may result in improvements in peripheral resistance, renin release, and cellular hypoxia. However, studies on the clinical benefits of pulsatile perfusion are inconclusive. Complications that may occur during operation of either type of pump include loss of electricity; loss of the ability to control pump speed, producing "runaway pump" or "pump creep" when turned off; loss of the flowmeter or revolutions per minute (RPM) indicator; rupture of tubing in the roller pump raceway; and reversal of flow by improper tubing in the raceway. A means to provide pumping manually in case of electrical failure should always be available.

## VENOUS RESERVOIR

The venous reservoir serves as a receiving chamber for venous return; facilitates gravity drainage; is a venous bubble trap; provides a convenient place to add drugs, fluids, or blood; and adds storage capacity for the perfusion system. During full CPB, as much as 1 to 3 L of blood may be stored in the reservoir, depending somewhat on the patient's preoperative volume status. Reservoirs may be rigid (hard) plastic canisters ("open" types) or soft, collapsible plastic bags ("closed" types). The rigid canisters facilitate volume measurements and the management of venous air, often have larger capacity, are easier to prime, permit suction for vacuum-assisted venous drainage, and may be less expensive. Soft bag reservoirs minimize the blood–gas interface and reduce the risk of pumping massive air emboli. A closed system is preferred to avoid the large amount of air–blood contact in open systems.

## OXYGENATORS

Membrane oxygenators are most commonly used and imitate the natural lung by interspersing a thin membrane of either microporous polypropylene (0.3- to 0.8-μm pores) or silicone rubber between the gas and the blood phases. Compared with bubble oxygenators, membrane oxygenators are safer, produce less particulate and gaseous microemboli, are less reactive to blood elements, and allow superior control of blood gases. The plasma-filled pores prevent gas from entering blood but facilitate transfer of both oxygen and $CO_2$. The most popular design uses sheaves of hollow fibers (120–200 μm) connected to inlet and outlet manifolds within a hard-shell jacket. Arterial $P_{CO_2}$ is controlled by gas flow, and $P_{O_2}$ is controlled by the fraction of inspired oxygen ($FIO_2$) produced by an air-oxygen blender, which also adds in variable amounts of volatile anesthetics. Modern membrane oxygenators add up to 470 mL of $O_2$ and remove up to 350 mL of $CO_2$ at 1 to 7 L of flow with priming volumes of 220 to 560 mL. Most units combine a venous reservoir, heat exchanger, and hollow-fiber membrane oxygenator into one compact unit.

Bubble oxygenators are obsolete in most Western countries but are used elsewhere for short-term CPB because of their low cost and good efficiency. Because each bubble presents a new foreign surface to which blood elements react, bubble oxygenators cause progressive injury to blood elements and entrain more gaseous microemboli. In bubble oxygenators, venous blood drains directly into a chamber into which oxygen is infused through a diffusion plate that produces thousands of small oxygen bubbles within the blood. Gas exchange occurs across a thin film at the blood–gas interface around each bubble. Bubbles and blood are separated by settling, filtration, and defoaming surfactants in a reservoir. Commercial bubble oxygenators incorporate a reservoir and heat exchanger within the same unit and are placed upstream to the arterial pump.

## HEAT EXCHANGERS

Heat exchangers control body temperature by heating or cooling the blood passing through the perfusion circuit. Frequently, hypothermia is used during cardiac surgery to reduce oxygen demand or facilitate operative exposure by temporary circulatory arrest. Gases are more soluble in cold than in warm blood; therefore, rapid rewarming of cold blood in the circuit or body may cause the formation of bubble emboli. Most membrane oxygenator units incorporate a heat exchanger upstream of the oxygenator so as to minimize bubble emboli. Blood is not heated above 40°C to prevent denaturation of plasma proteins, and temperature differences within the body and perfusion circuit are limited to 5°C to 10°C to prevent bubble emboli. The heat exchanger may be supplied by hot and cold tap water, but separate heater/cooler units with convenient temperature-regulating controls are preferred.

## FILTERS

Filters are universally used within CPB circuits to prevent both macro- and microemboli, which, in both gaseous and particulate form, likely produce much of the morbidity

associated with cardiac operations using CPB. As compared with no filter, studies indicate that all commercially available filters effectively remove gaseous and particulate emboli. Most investigations find that the Dacron wool depth filter is most effective, particularly in removing micro- and macroscopic air. Pressure differences across filters vary between 24 and 36 mm Hg at a flow of 5 L/min. Filters cause slight hemolysis and tend to trap some platelets.

Because of significant debris present within cardiotomy suction blood, the need for microfilters in the cardiotomy suction reservoir is universally accepted, and most commercial units contain an intergrated micropore filter. Most circuits also contain an arterial line filter of some type, although efficacy in this location remains unsettled. These filters are usually also of the Dacron wool type and must be used with a bypass line during priming to purge trapped air. Leukocyte-depleting arterial filters have not been proven effective at limiting the inflammatory response or other complications.

## CARDIOTOMY RESERVOIR AND FIELD SUCTION

Blood aspirated from the surgical wound may be directed to the cardiotomy reservoir for defoaming, filtration, and storage before it is added directly to the perfusate. A sponge impregnated with a surfactant removes bubbles by reducing surface tension at the blood interface, and macro-, micro-, or combined filters remove particulate emboli. Negative pressure is generated by either a roller pump or vacuum applied to the rigid outer shell of the reservoir. The degree of negative pressure and blood level must be monitored to avoid excessive suction or introducing air into the perfusate.

The cardiotomy suction and reservoir are major sources of hemolysis, particulate and gaseous microemboli, fat globules, cellular aggregates, platelet injury and loss, cytokine-generated thrombin formation, and fibrinolysis. Air aspirated with wound blood contributes to blood activation and destruction and is difficult to remove because of the high proportion of nitrogen, which is poorly soluble in blood. High suction volumes and the admixture of air are particularly destructive of platelets and red cells. Commercial reservoirs are designed to minimize air entrainment and excessive injury to blood elements. The removal of air and microemboli is also facilitated by allowing aspirated blood to settle within the reservoir before it is added to the perfusate.

An alternative method for recovering field-aspirated blood is to dilute the blood with saline and then remove the saline to return only packed red cells to the perfusate. Centrifugal cell washers automate this process and remove air, thrombin, and nearly all biologic and nonbiologic microemboli from the aspirate at the cost of discarding plasma. A third alternative is to discard all field-aspirated blood. Increasingly, field-aspirated blood is recognized as a major contributor to the thrombotic, bleeding, and inflammatory complications of CPB.

## VENTS AND DECOMPRESSION OF THE HEART

During CPB, blood escaping atrial or venous cannulas and from the coronary sinus and Thebesian veins may pass through the unopened right heart into the pulmonary circulation. This blood plus bronchial venous blood, blood regurgitating through the aortic valve, and blood from undiagnosed abnormal sources (patent foramen ovale, patent ductus, etc.) may distend the left ventricle. Venting of the heart during CPB aids in myocardial protection by preventing ventricular distention and keeping warm blood out of the heart during hypothermic cardioplegic arrest. Ventricular overdistention can be a particularly serious problem in the presence of severe aortic valvular insufficiency.

There are several methods for venting the left heart during cardiac arrest. The most common techniques include placement of a multihole catheter from the right superior pulmonary vein across the mitral valve; use of an aortic root vent, often in combination with an antegrade cardioplegia catheter; placement of a suction catheter in the main pulmonary artery, which decompresses the left atrium across the pulmonary capillary bed; and, less commonly, placement of a suction catheter directly into LV apex. Vent catheters are drained to the cardiotomy reservoir, usually by a dedicated roller pump. The most common complication of left heart venting is residual air when the heart is filled and begins to contract. De-airing maneuvers (Table 24-1)—such as manual displacement, Valsalva breaths, and TEE detection of residual pockets—are important methods for ensuring its removal.

## CARDIOPLEGIA DELIVERY SYSTEMS

Cardioplegic solutions are delivered through a separate perfusion system, which includes a reservoir, heat exchanger, roller pump, bubble trap, and perhaps microfilter. The system may be completely independent of the main perfusion circuit, or it may branch from the arterial line. The system may also be configured to vent the aortic root between infusions.

**TABLE 24-1: Strategies for Management of Intracardiac Air**

| |
|---|
| Preventive measures |
| Limited use of vents |
| Vents off or on low suction while aorta or heart chamber is open |
| Instillation of $CO_2$ into the operative field |
| De-airing maneuvers |
| Aortic venting during and after cross-clamp release |
| Needle aspiration of left ventricular apex |
| Valsalva breaths |
| Rotation of operating table |
| Manual dislodgment, e.g., inversion of left a trial appendage |
| Maintenance of partial cardiopulmonary bypass with left ventricular ejection |

## HEMOCONCENTRATORS

Hemoconcentrators, like oxygenators, contain one of the several available semipermeable membranes (typically hollow fibers) that transfer water, electrolytes (e.g., potassium), and molecules up to 20 kDa out of the blood compartment. Hemoconcentrators may be connected to either venous or arterial lines or a reservoir in the main perfusion circuit, but they require high pressure in the blood compartment to effect fluid removal. Thus, a roller pump is needed unless the unit is connected to the arterial line. Suction may or may not be applied to the air side of the membrane to facilitate filtration. At flows from 500 mL/min, up to 180 mL/min of fluid can be removed. Hemoconcentrators conserve platelets and most plasma proteins as compared with centrifugal cell washers and may allow greater control of potassium concentrations than is possible with the use of diuretics. Aside from cost, disadvantages are few and adverse effects rare.

## CONDUCT OF CARDIOPULMONARY BYPASS

The performance of CPB requires constant interaction between the surgeon, the perfusionist, and the anesthesiologist, especially during periods of transition to and from artificial perfusion. Although frequent dialogue is important, often a member of the team, usually the surgeon, may be focused on other aspects of the operation and unavailable to discuss nonemergent aspects of perfusion in a particular case. For this reason, written protocols and procedures developed in a multidisciplinary fashion are important for ensuring the safe conduct of CPB.

## ASSEMBLY OF THE CPB CIRCUIT

The perfusionist is responsible for setting up and preparing the heart–lung machine and all components necessary for the proposed operation. Most perfusionists use commercial, sterile, preprepared, and customized tubing packs, which are connected to the various components that constitute the heart–lung machine. This dry assembly takes about 10 to 15 min; the unit can then be kept in standby for up to 7 days. Once the system is primed with fluid, which takes about 15 min, it should be used within 8 h. After assembly, the perfusionist conducts a safety inspection and completes a written prebypass checklist.

## PRIMING

Adult extracorporeal perfusion circuits require 1.5 to 2.0 L of balanced electrolyte solution (lactated Ringer's solution, Normosol-A, or Plasma-Lyte). Before connections are made to the patient, the prime is recirculated through a micropore filter to remove particulates and air emboli. The priming volume represents approximately 30 to 35 percent of the patient's blood volume and reduces the hematocrit to about two-thirds of the preoperative value. Hemodilution is an important cause of intraoperative and postoperative anemia. Priming requirements can be reduced by using smaller-diameter and shorter tubing lengths and operating the machine with minimal perfusate in the venous and cardiotomy reservoirs. Autologous blood prime, usually with retrograde venous blood into the pump, is another method to reduce crystalloid priming volume, but this risks hypovolemic sequelae prior to the initiation of CPB. Improvements in clinical outcomes have not been definitively proven with these techniques.

The use of colloids (albumin, gelatins, dextrans, and hetastarches) in the priming volume is controversial. Colloids reduce the fall in colloid osmotic pressure and may reduce the amount of fluid entering the extracellular space. However, prospective clinical studies have failed to document significant clinical benefits with albumin, which is expensive and may have adverse effects.[9,10] Hetastarch may contribute to postoperative bleeding.

## ANTICOAGULATION AND REVERSAL

Porcine heparin (300–400 U/kg IV) is given before arterial or venous cannulas are inserted, and CPB is not started until anticoagulation is confirmed by activated clotting time (ACT). Most would agree that the minimum ACT to begin CPB is 400 s, but many groups prefer a goal of 480 s because heparin only partially inhibits thrombin formation during CPB. Inadequate anticoagulation risks thrombosis of the circuit at the extreme end of the spectrum, but it may also result in less dramatic consumption of clotting factors and postoperative coagulopathy. Excessively high concentrations of heparin (ACT >1000 s) may cause remote bleeding away from operative sites.

Failure to achieve a satisfactory ACT may be due to inadequate heparin or to low concentrations of circulating antithrombin. If a total of 500 U/kg of heparin fails to prolong ACT adequately, fresh frozen plasma or recombinant antithrombin is needed to increase antithrombin concentrations and overcome "heparin resistance," a phenomenon more commonly seen in patients on preoperative intravenous heparin therapy.

Antifibrinolytic agents such as aminocaproic acid or tranexamic acid are routinely used during CPB and have been shown to improve postoperative chest tube drainage but not clinical outcome. Another pharmacologic strategy to reduce bleeding complications is the use of aprotinin, a serine-protease inhibitor with general anti-inflammatory properties. Extensive literature exists on the beneficial effects of aprotinin on a variety of clinical outcome measures, especially with reoperative cardiac surgery.[11] The most important of these benefits may be a reduction in the risk of stroke, noted in a large retrospective analysis.[12] Drawbacks to aprotinin include significant cost and possibly an adverse effect

on renal function in the presence of angiotensin converting enzyme inhibitors.[13] In 2008, the results of the blood conservation using antifibrinolytics in a randomized trial (BART) trial, a randomized-prospective study on the use of aprotinin in cardiac surgery, was published and demonstrated excess rates of renal failure and mortality with aprotinin.[14] Since then, this drug has minimal availability and usage. During CPB, the ACT is measured every 30 min. If the ACT goes below the target level, more heparin is given. Usually, one-third of the initial heparin bolus is given every hour even when the ACT is within the normal range. Hepcon tests, which measure heparin concentration, may also be used; although, their results are more reproducible than ACT, ACT is less time-consuming and provides satisfactory monitoring of anticoagulation.

One milligram of protamine (not to exceed 3 mg/kg) is given for each 100 U of heparin injected in the initial bolus dose. The heparin–protamine complex activates complement and often causes acute hypotension, which may be attenuated by adding calcium (2 mg/1 mg protamine). After one-third of the planned protamine dose has been administered, blood must not be returned to the cardiotomy reservoir from the surgical field. Rarely, protamine may cause an anaphylactic reaction in patients with antibodies to protamine insulin. Neutralization of heparin is usually confirmed by an ACT or Hepcon test, and more protamine (50 mg) is given if either of the tests remains prolonged and bleeding is a problem. "Heparin rebound" is the term used to describe a delayed heparin effect due to the release of tissue heparin after protamine is cleared from the circulation. Although protamine is a mild anticoagulant, one or two supplemental 25- to 50-mg doses can be given empirically if heparin rebound is suspected. In most instances, the heart–lung machine should be available for immediate use until the patient leaves the operating room.

## STARTING CPB

CPB is started at the surgeon's request with concurrence of the anesthesiologist and perfusionist. As venous return enters the machine, the perfusionist progressively increases arterial flow while monitoring the patient's blood pressure and volume levels in all reservoirs. Important observations include adequacy of venous drainage, acceptable flow rates, acceptable arterial line pressure, oxygenation of arterial blood, appropriate systemic arterial pressure, and adequate decompression of the heart. Once full stable CPB is established, lung ventilation is discontinued, systemic cooling may begin, and the aorta may be clamped for arresting the heart.

## CARDIOPLEGIA

After aortic cross-clamping, cardiac arrest is usually achieved with antegrade blood or crystalloid cardioplegia administered directly into the aortic root by a dedicated cardioplegia roller pump. The heart usually arrests within 30 to 60 s. A delay may indicate problems with delivery of the solution, incomplete aortic occlusion, or unrecognized aortic regurgitation. Retrograde cardioplegia is often given after an antegrade dose to facilitate cardioplegia delivery distal to atherosclerotic stenoses of the coronary arteries. In contrast to antegrade cardioplegia, epicardial and intracardiac procedures are not much hindered by delivery of retrograde cardioplegia. The usual flow of retrograde cardioplegia is 200 to 400 mL/min at coronary sinus pressures between 30 and 50 mm Hg. Induction of electrical arrest is slower (2–4 min) than with antegrade, and retrograde cardioplegia may provide incomplete protection of the right ventricle.

## DETERMINANTS OF SAFE PERFUSION

### Blood Flow Rate

The generally accepted flow rate at 35°C to 37°C and hematocrit of 25 percent is approximately 2.4 L/min/$m^2$ in deeply anesthetized and muscle-relaxed patients. Hemodilution reduces blood oxygen content and dictates that flow rate must increase over resting normal cardiac output or oxygen demand must decrease. As long as mean arterial pressure remains above 50 to 60 mm Hg (i.e., above the autoregulatory range), cerebral blood flow is preserved even if systemic flow is less than normal. However, as total systemic flow is progressively reduced, there is a hierarchal reduction of flow to other organs. First skeletal muscle flow falls, then flow to the abdominal viscera and bowel, and finally flow to the kidneys.

### Arterial Pressure

Systemic arterial blood pressure is a function of flow rate, blood viscosity (hematocrit), and vascular tone. Perfusion of the brain is normally protected by autoregulation, which appears to be lost somewhere between 55 and 60 mm Hg during CPB at moderate hypothermia and 24 percent hematocrit. This pressure is thus generally regarded to be the lowest safe pressure for routine CBP. In older patients, who may have vascular disease and/or hypertension, mean arterial blood pressure is generally maintained between 70 and 80 mm Hg at 37°C. Higher pressures are undesirable because collateral blood flow to the heart and lungs increases blood in the operative field. Hypotension during CPB may be due to low pump flow, aortic dissection, measurement error, or vasodilatation. Phenylephrine is most often used to elevate blood pressure, but arginine vasopressin (0.05–0.1 U/min) may also be used. If anesthesia is adequate, hypertension is generally treated by nitroprusside or nitroglycerin.

Mean blood pressure is an important perfusion parameter in nonpulsatile CPB, the most common mode of perfusion. Pulsatile CPB theoretically reduces vasoconstrictive reflexes and neuroendocrine responses and may increase oxygen

consumption, reduce acidosis, and improve organ perfusion. Effective generation of pulse pressure, however, requires a larger-diameter aortic cannula and higher nozzle velocities, which may increase trauma to blood elements.

### Hematocrit

The ideal hematocrit during CPB remains controversial because of competing advantages and disadvantages.[15,16] Low hematocrits reduce blood viscosity and hemolysis, reduce oxygen-carrying capacity, and reduce the need for blood transfusion. Hypothermia reduces oxygen consumption and permits perfusion at 26°C to 28°C with hematocrits between 18 and 22 percent; at higher temperatures, however, limits on pump flow may not satisfy oxygen demand. Neurologic and renal function appear to be most susceptible to damage with low hematocrits, a problem that may be overcome with increasing pump flows to maintain adequate oxygen delivery.[17] A good generalization is that hematocrit should not be maintained below 22 to 24 percent.

### Temperature

The ideal temperature for uncomplicated adult cardiac surgery is controversial, although most routine adult cardiac operations are performed with mild systemic hypothermia (28°C–32°C). This allows for some organ protection by means of reduced cellular metabolism but avoids complications associated with lower temperatures, such as interference with enzyme and organ function, increased systemic vascular resistance, delays in cardiac recovery, lengthened duration of CPB, and increased risk of cerebral hyperthermia with rewarming. Increasingly, efforts are made to avoid cerebral hyperthermia during and after operation.

### Acid/Base Management

There are two strategies for managing blood pH during hypothermia: pH-stat and alpha-stat. In adults, alpha-stat may be better for neurologic protection, as the microembolic burden may be lessened. pH-stat maintains temperature-corrected pH 7.40 at all temperatures and requires the addition of $CO_2$ as the patient is cooled. Alpha-stat allows the pH to increase during cooling, so that blood becomes alkalotic. Cerebral blood flow is higher, while pressure is passive and uncoupled from cerebral oxygen demand with pH-stat. With alpha-stat, cerebral blood flow is lower, autoregulated, and coupled to cerebral oxygen demand.

## PATIENT MONITORING

Systemic arterial pressure is typically monitored by radial, brachial, or femoral arterial catheter; central venous pressure is routinely monitored by a jugular venous catheter. Routine use of a Swan–Ganz pulmonary arterial catheter is controversial and not necessary for uncomplicated operations in low-risk patients. Bladder or rectal temperature is usually used to estimate the temperature of the main body mass but does not reflect brain temperature, which is estimated by nasopharyngeal or tympanic membrane sensors. The jugular venous bulb temperature is considered the best surrogate for brain temperature but is more difficult to obtain.

TEE examination is an important monitor during most applications of CPB[18,19] to assess catheter and vent insertion and location, severity of aortic atherosclerosis, myocardial injury, infarction, dilatation, contractility, thrombi and residual air, valve function after repair or replacement, diagnosis of dissection, and adequacy of de-airing at the end of CPB.

Mixed venous oxygenation ($SvO_2$), which assesses the relationship between $DO_2$ and $VO_2$, is monitored on the CPB circuit. $SvO_2$ below 60 percent indicates inadequate oxygen delivery; but because of differences in regional vascular tone, higher $SvO_2$ does not assure adequate oxygen delivery to all vascular beds. When adequacy of perfusion is questionable, more frequent blood gas monitoring should be performed to assess for metabolic acidosis.

## TERMINATION OF CPB

Discontinuation of CPB involves a complex interplay of physiologic manipulation and operating room personnel. Requirements for termination of CPB include physiologic systemic temperature, adequate heart and lung function, acceptable acid–base and electrolyte status, and no trapped intracardiac air. De-airing maneuvers are important to prevent coronary embolization and cardiac failure (Table 24-1). Once preparations are completed, surgeon, anesthesiologist, and perfusionist begin to wean the patient off CPB. The perfusionist gradually occludes the venous line and simultaneously reduces pump input as cardiac rate and rhythm, arterial pressure and pulse, and central venous pressure are monitored and adjusted. Initially blood volume within the pump is kept constant, but as pump flow approaches zero, volume is added or removed from the patient to produce arterial and venous pressures within the physiologic ranges. During weaning, cardiac filling and contractility is often monitored by TEE, and intracardiac repairs and regional myocardial contractility are assessed. Pulse oximetry saturation near 100 percent, end-tidal $CO_2$ >25 mm Hg, and mixed venous oxygen saturation >65 percent confirm satisfactory ventilation and circulation. When cardiac performance is satisfactory and stable, all catheters and cannulas are removed, protamine is given to reverse heparin, and blood return from the surgical field is discontinued. Once the patient is hemodynamically stable as determined by surgeon and anesthesiologist and after starting wound closure, the perfusate may be returned to the patient in several ways. The entire perfusate may be washed and returned as

packed cells, or excess fluid may be removed by a hemoconcentrator. At least some of the perfusate, which still contains heparin and coagulation factors, is gradually pumped into the patient to maintain intravascular volume, which can fluctuate significantly after separation from CPB. Occasionally, some of the perfusate must be bagged and given later. The circuit should not be completely disassembled until the chest is closed and the patient is ready for transfer.

## CIRCUIT COMPLICATIONS

Life-threatening incidents occur in 0.4 to 2.7 percent of operations with CPB. Massive air embolism, aortic dissection, dislodgement of cannulas, and clotting within the circuit during perfusion are the principal causes of serious injury or death. Malfunction of the heater-cooler, oxygenator, pumps, and electrical supply are the most common threatening incidents related to equipment. Other threatening incidents include premature takedown or clotting within the perfusion circuit. Complications related to connections to and from the heart–lung machine and perfusion during operation are described above, with descriptions of the various components of the perfusion circuit.

## METABOLIC COMPLICATIONS AND ORGAN INJURY

Depending on the degree of investigation, untoward systemic and organ-specific effects of CPB can be found in essentially all patients placed on the pump. Minor complications predominate, but in 0.1 to 0.5 percent, serious and life-threatening events can be attributed to the effects of CPB (Table 24-2).

**TABLE 24-2: Adverse Manifestations of CPB**

| | Common and Mild | Uncommon and Severe |
|---|---|---|
| Systemic | SIRS | Multiorgan failure |
| Cardiac | Tachycardia, a trial arrhythmias | Low-cardiac-output state, ventricular arrhythmias |
| Pulmonary | Mild hypoxia, tachypnea | ARDS |
| Neurologic | Anxiety, drowsiness, neuropsychological deficit | Delirium, encephalopathy, stroke |
| Renal | Oliguria, <50% increase in serum creatinine | Acute renal failure |
| Gastrointestinal | Nausea, vomiting, anorexia | Ileus, perforation, stress gastritis, pancreatitis |
| Hepatic | Mild serum transaminase and bilirubin elevation | Jaundice, fulminant liver failure |
| Hematologic | Anemia, mild thrombocytopenia, leukocytosis | HIT with thrombosis, disseminated intravascular consumption |

SIRS, systemic inflammatory response syndrome; ARDS, acute respiratory distress syndrome; HIT, heparin-induced thrombocytopenia.

## GENERAL MECHANISMS AND THE SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

CPB preempts normal reflex and chemoreceptor control of the circulation, initiates coagulation, generates vasoactive and cytotoxic substances, and produces a variety of microemboli. Ischemia/reperfusion is also an important cause of reversible and irreversible cell injury and may not be detected because regional hypoperfusion may not be evident. Regional perfusion is also influenced by acid–base relationships during cooling and may affect postoperative organ function. Temperature differences within the body and within organs produce regional temperature-perfusion mismatch, which can precipitate regional hypoperfusion and acidosis due to inadequate oxygen delivery. There is no method to monitor regional perfusion during CPB, and even direct temperature surveillance of vital organs may fail to detect temperature differences within the organ.

The subsequent inflammatory response produces the terminal complement attack complex, anaphylatoxins, cytotoxic proteases, collagenases, metalloproteinases, reactive oxidants, endotoxin, and activated neutrophils and monocytes, which can destroy nonhost organisms as well as tissue cells. These agents directly access the specialized cells of every organ by passing between endothelial cell junctions to reach the interstitial compartment. Reduced plasma colloid osmotic pressure, elevated venous pressure, and widened endothelial cell junctions increase the volume of the interstitial space during CPB in proportion to the duration of bypass, magnitude of the dissection, transfusions, and other factors. In prolonged bypass runs, the interstitial compartment may increase from 18 to 33 percent, but intracellular water does not increase during CPB.

The systemic inflammatory response syndrome (SIRS) can be detected to some degree in nearly all patients subjected to a pump-oxygenator. Clinically, this is manifest as fevers, leukocytosis, tachypnea, tachycardia in the non–beta-blocked heart, as well as fatigue, malaise, anorexia, and nausea. Elevated levels of circulating catecholamines are also present and contribute to the development of atrial and ventricular arrhythmias. Besides exposure to the circuit, other factors contributing to the development of SIRS include anemia and blood

transfusions, hypotension, surgical trauma, pain, and preexisting patient factors such as infection or advanced heart failure. Strategies to limit the severity of SIRS are thus aimed at minimizing time on pump, avoiding other precipitating factors, and medical optimization of the patient prior to surgery. No pharmacologic strategies are effective in prevention.

## MICROEMBOLIZATION

Microemboli, which are defined as particles <500 μm in diameter, that enter the circulation during CPB are important causes of regional ischemia. Air entry into the perfusion circuit produces the most dangerous gas emboli because nitrogen is poorly soluble in blood and is not a metabolite. Carbon dioxide is rapidly soluble in blood and is sometimes used to flood the surgical field to displace air. Foreign emboli, largely generated in the surgical wound, reach the circulation from the surgical field via the cardiotomy reservoir. The cardiotomy reservoir is the primary source of foreign emboli and the major source of blood-generated emboli, particularly fat emboli.[20] Extensive activation and physical damage to blood elements produce a wide variety of emboli, which tend to increase with the duration of perfusion.

The principal methods for reducing circulating microemboli include the following: adequate anticoagulation, membrane oxygenator, washing blood aspirated from the surgical wound,[21] filter in the cardiotomy reservoir, secure purse-string sutures around cannulas, strict control of all air entry sites within the perfusion circuit, removal of residual air from the heart and great vessels, and avoidance of atherosclerotic emboli.

Many intraoperative strategies are available to reduce cerebral atherosclerotic embolization. These include routine epicardial echocardiography of the ascending aorta to detect both anterior and posterior atherosclerotic plaques and sites free of atherosclerosis for placing the aortic cannula. Recently, special catheters with or without baffles or screens have been developed to reduce the number of atherosclerotic emboli that reach the cerebral circulation.[22,23] In patients with moderate or severe ascending aortic atherosclerosis, a single application of the aortic clamp as opposed to partial or multiple applications is strongly recommended and has been shown to reduce postoperative neuronal and neurocognitive deficits in a large clinical series.[24] In these patients, retrograde cardioplegia is preferred over antegrade cardioplegia to avoid a sandblasting effect of the cardioplegic solution. No aortic clamp may be safe or even possible in some patients with severe atherosclerosis or "porcelain aorta," and other techniques may be required (see "Special Topics"). Filter placement within the CPB circuit is likely an important step to prevent emboli. However, air and fat can pass through filters and air and atherosclerotic emboli may enter the circulation downstream of the filter.

## SPECIFIC ORGAN INJURY

### Cardiac Injury

It is difficult to separate postoperative cardiac dysfunction from injury due to CPB, ischemia/reperfusion, direct surgical trauma, the disease being treated, and inadequate myocardial protection. The heart, like all organs and tissues, is subject to microemboli, protease and chemical cytotoxins, activated neutrophils and monocytes, and regional hypoperfusion during CPB. Some degree of myocardial "stunning" during the period when coronary blood flow is interrupted is inevitable, as is some degree of reperfusion injury after ischemia. Both myocardial edema and distention of the flaccid cardioplegic heart during aortic cross-clamping reduce myocardial contractility. Last, if myocardial contractility is weak, excessive preload or high afterload during weaning from CPB will increase ventricular end-diastolic volume, myocardial wall stress, and oxygen consumption. Thus, the postoperative performance of the heart depends on many variables and not just the injuries produced by CPB.

### Neurologic Injury

The brain is the most sensitive organ exposed to damage by CPB and also the most important organ to protect. Even small injuries may produce detectable, functional losses that are not detectable or important in other organs. Regional hypoperfusion, edema, microemboli, and circulating cytotoxins may cause subtle losses in cognitive function, behavioral patterns, and physiologic and physical function that can pass unnoticed, be accepted and dismissed, or profoundly compromise the patient's quality of life. The most obvious neuropsychologic abnormalities are coma, delirium, and confusion, but often transitory episodes of delirium and confusion are dismissed as due to anesthesia or medications. More subtle losses are determined by comparison of preoperative and postoperative performance using a standard battery of neuropsychologic tests.

Advancing age increases the risk of stroke or cognitive impairment, especially after the age of 60, at least in part because other risk factors for neurologic injury also increase with age. Hypertension and diabetes occur in approximately 55 and 25 percent of cardiac surgical patients, respectively. Fifteen percent have carotid stenosis of 50 percent or greater, and up to 13 percent have had a transient ischemic attack or prior stroke. The severity of atherosclerosis in the ascending aorta as detected by epiaortic ultrasound scanning adds to the risk of stroke or cognitive dysfunction. Palpable ascending aortic atherosclerotic plaques markedly increase the risk of right carotid arterial emboli as detected by Doppler ultrasound.[25] The incidence of severe aortic atherosclerosis is 1 percent in cardiac surgical patients below 50 years and is 10 percent in those between 75 and 80 years.

Mechanisms of cerebral injury during CPB are microemboli and hypoperfusion, which are to some extent mutually exclusive. Microemboli are distributed in proportion to blood flow; thus reduced cerebral blood flow reduces microembolic injury but increases the risk of hypoperfusion.[26] In clinical practice, air, atherosclerotic debris, and fat are the major types of microemboli causing brain injury and all cause neuronal necrosis by blocking small cerebral vessels. Massive air embolism causes a large ischemic injury, but gaseous cerebral microemboli may directly damage endothelium in addition to blocking blood flow.

Besides protecting against embolic events, recommended conditions for protecting the brain during CPB include mild hypothermia (32°C–34°C) and a hematocrit above 25 percent. Temporary increases in cerebral venous pressure caused by SVC obstruction and excessive rewarming above blood temperatures of 37°C should be avoided. Barbiturates reduce cerebral metabolism by decreasing spontaneous synaptic activity and provide a definite neuroprotective effect during clinical cardiac surgery using CPB. Unfortunately, these agents delay emergence from anesthesia and prolong ICU stays. Although the use of aprotinin has been associated with fewer strokes in retrospective analysis, currently no agent is strongly recommended for protection of the central nervous system during CPB.

Off-pump myocardial revascularization theoretically avoids many of the causes of cerebral injury due to CPB, but, as noted above, many causes of neuronal injury are independent of CPB and related to atherosclerosis and the entry of air into the circulation. Measurements of carotid emboli by Doppler ultrasound indicate fewer emboli and improved neurocognitive outcomes in patients who have off-pump surgery as compared to those with on-pump revascularization.[27,28] Unfortunately, metanalyses of randomized trials comparing on- and off-pump CABG have not demonstrated a definitive reduction in stroke risk.[29,30]

## Lung Injury

Hypoxia of some degree is a nearly universal finding after CPB. Patient factors and the separate effects of operation and CPB combine to compromise lung function early after operation. Chronic smoking and emphysema are the most common patient factors, but muscular weakness, chronic bronchitis, occult pneumonia, preoperative pulmonary edema, and unrelated respiratory disease are other contributors to postoperative pulmonary dysfunction. Incisional pain, lack of movement, shallow respiratory sighs, reduced pulmonary compliance, weak cough, increased pulmonary arteriovenous shunting, and interstitial edema, to some degree, are consequences of anesthesia and any operation. CPB significantly adds to this injury.

During CPB, the lungs are supplied by the bronchial arteries and pulmonary arterial blood flow may be absent or minimal. Whether or not alveolar cells suffer an ischemia/reperfusion injury is unclear, but the lungs are subject to many insults that combine to increase pulmonary capillary permeability and interstitial lung water. Hemodilution, reduced plasma oncotic pressure, and temporary elevation of left atrial or pulmonary venous pressure during CPB or during weaning from CPB increase extravascular lung water. Microemboli and circulating cellular, vasoactive, and cytotoxic mediators of the inflammatory response reach the lung via bronchial arteries during CPB and with resumption of the pulmonary circulation during weaning. These agents increase pulmonary capillary permeability, perivascular edema, and bronchial secretions and perhaps cause observed changes in alveolar surfactant. All of these changes combine to enhance regional atelectasis, increase susceptibility to infection, and increase the physiologic arteriovenous shunt, which reduces systemic arterial $PaO_2$.

Postoperative respiratory care is based on restoring normal pulmonary capillary permeability and interstitial lung volume, preventing atelectasis, reinflating atelectatic segments, maintaining normal arterial blood gases, preventing infection, and facilitating removal of bronchial mucus. Improved postoperative respiratory care, an understanding of the mechanisms of lung injury during CPB, and efforts to prevent or control the causes of injury can markedly reduce the incidence of pulmonary complications.

## Renal Injury

Some degree of renal injury is inevitable during CPB, and postperfusion proteinuria occurs in all patients. The incidence of acute renal failure requiring dialysis after CPB is 1 to 5 percent, depending on the complexity of surgery and preoperative factors. As with other organs, the preoperative health of the kidneys is a major factor in the ability of that organ to withstand the microembolic, cellular, and regional malperfusion injuries caused by CPB. Risk factors for postoperative renal dysfunction include age over 70, diabetes mellitus, previous cardiac surgery, congestive heart failure, and a complex, prolonged operation. Hemoglobin is toxic to renal tubules and its precipitation can block both blood and urine flow to the tubules. Hemodilution dilutes plasma hemoglobin; improves flow to the outer renal cortex; improves total renal blood flow; increases creatinine, electrolyte, and water clearance; and increases glomerular filtration and urine volume.

Perioperative periods of low cardiac output and/or hypotension added to the microembolic, cellular, and cytotoxic injuries of CPB and to any preoperative renal disease are the major cause of postoperative renal failure. Low cardiac output reduces renal perfusion pressure and causes angiotensin II production and renin release, which further decreases renal blood flow. Kidneys, already compromised by preoperative disease and the CPB injury, are particularly sensitive to ischemic injury secondary to low cardiac output and hypotension. Thus perioperative management includes efforts to maximize cardiac output using dopamine or dobutamine if necessary, avoiding renal arterial vasoconstrictive drugs,

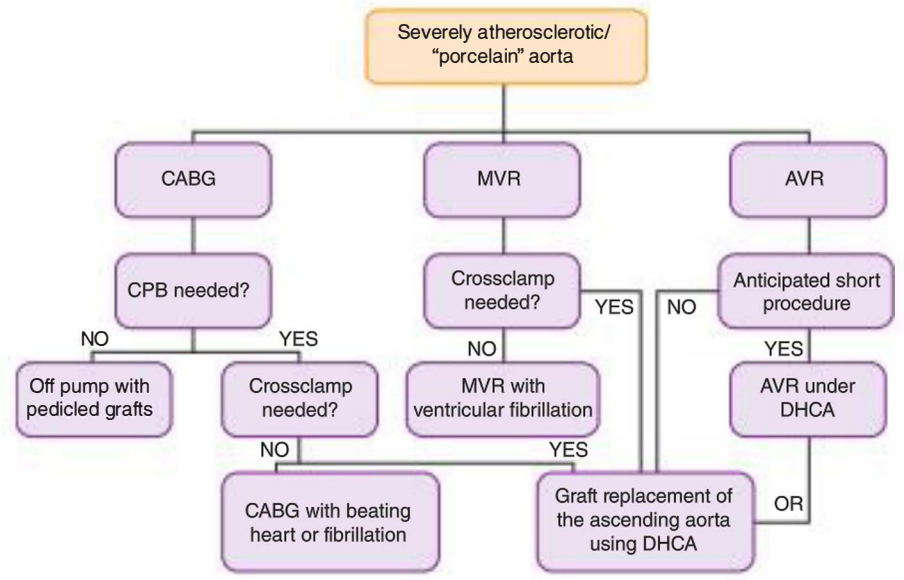



**FIGURE 24-3** Algorithm for management of the severely atherosclerotic ascending aorta.

providing adequate crystalloid infusions to maintain urine volume, and alkalinizing urine to minimize the precipitation of tubular hemoglobin if excessive hemolysis has occurred. Unfortunately, no pharmacologic strategies have proven beneficial in protecting renal function after CPB.

### Pancreatic Injury

Less than 1 percent of patients develop clinical pancreatitis after CPB, but approximately 30 percent develop a transitory, asymptomatic increase in plasma amylase and/or lipase. A history of recurrent pancreatitis, perioperative circulatory shock or hypotension, excessively prolonged CPB, and continuous, high doses of inotropic agents are risk factors for the development of postoperative clinically relevant pancreatitis. Experimentally and clinically, high doses of calcium increase intracellular trypsinogen activation and histologic evidence of pancreatitis. Fulminant pancreatits is very rare but often fatal.

## SPECIAL TOPICS

### The "Bad Aorta"

Some degree of atherosclerosis of the ascending aorta is a common finding during cardiac surgery. Simple palpation can often detect local areas of plaque that must be avoided in cannulating, clamping, or manipulating the aorta. Epiaortic scanning is more sensitive for the detection of ascending aortic atherosclerosis and is preferred for all patients who have a history of transient ischemic attack, stroke, severe peripheral vascular disease, palpable calcification in the ascending aorta, calcified aortic knob on chest radiograph, age above 50 to 60 years, or TEE findings of moderate aortic atherosclerosis.[31]

Some findings on examination of the aorta can dramatically alter the conduct of an operation. Calcified aorta (porcelain aorta), which occurs in 1 to 4 percent of patients, is one such finding. This condition increases the risks of dislodgement of atheromatous debris from the aortic wall due to manipulation, cross-clamping, or the sandblasting effect of the cannula jet and greatly increases the risks of perioperative stroke, aortic dissection, and postoperative renal dysfunction.[32] Many strategies exist for patient management in this setting; these depend on the surgeon's preference and the cardiac condition being treated (Fig. 24-3). For coronary artery bypass, the first question one must ask is "Is the pump necessary?" Conversion from on-pump to off-pump CABG is a good alternative, especially when manipulation of the ascending aorta can be completely avoided. In this scenario, pedicled single or sequential arterial grafts, T or Y grafts from a pedicled mammary artery, or vein grafts anastomosed to arch vessels can be used.

If CPB is deemed necessary, minimal manipulation of the aorta should remain a primary focus. Initially, the best site for cannulation must be determined. Femoral cannulation in this setting is usually not a good alternative because of the likely coexistence of severe atherosclerosis in the aortoiliac and femoral circulations. In contrast, the axillary artery is usually free of significant disease and is often a good alternative. Another option is cannulation of a "soft spot," if one exists, atraumatically on the ascending aorta or aortic arch.

Next, one must decide whether aortic cross-clamping is necessary. Many coronary operations can be performed

without a cross clamp on the empty, beating heart. Alternatively, ventricular fibrillation can be induced electrically or with hypothermia for coronary or mitral valve operations with cross-clamping. Finally, deep hypothermic circulatory arrest (DHCA) can be used to replace the aortic valve without ever placing a clamp.[33] If aortic cross-clamping is deemed necessary, DHCA can be used initially to replace the ascending aorta with a graft using an open technique. The graft can then be clamped for reinstitution of CPB and maintenance of cardiac arrest.

Severe aortic atherosclerosis is a risk factor for the still rare but dramatic complication of intra- or postoperative aortic dissection. The first clues may be discoloration beneath the adventitia near the cannula site, proximal vein anastomosis or clamp location, an increase in arterial line pressure, or a sharp reduction in return to the venous reservoir. TEE may be helpful in confirming the diagnosis, but prompt action is necessary to limit the dissection and maintain perfusion. If a localized dissection occurs immediately upon removing the cross clamp, the clamp should be reapplied to limit proximal and distal extension of the dissection flap. Local suture or partial graft repair is then performed. For more extensive dissections, the cannula must be promptly transferred to a peripheral artery or uninvolved distal aorta. Blood pressure should be controlled pharmacologically and perfusion cooling to temperatures less than 20°C initiated. During hypothermic circulatory arrest, the aorta is opened at the original site of cannulation and repaired by direct suture, patch, or circumferential graft. When dissection is recognized early, survival rates range from 66 to 85 percent, but when this problem occurs late or is discovered after operation, survival is approximately 50 percent.

## PERSISTENT LEFT SVC

The presence of a persistent left SVC (PLSVC) is rare but should be suspected when the left innominate vein is small or absent and a large coronary sinus or the PLSVC itself is seen on baseline TEE, as the PLSVC usually drains into the coronary sinus. A PLSVC may thus complicate retrograde cardioplegia or entry into the right heart. For epicardial operations, standard single- or two-stage venous cannulation remains effective, although retrograde cardioplegia cannot be used. For other cases, if an adequate-sized innominate vein is present (30 percent of patients), the PLSVC can simply be occluded during CPB and cerebral venous return will not be impeded. If the innominate vein is absent or small (about 75 percent of patients) or if the right SVC is not present, occlusion of the PLSVC may cause venous hypertension and possible cerebral injury. In these patients, the SVC may be cannulated directly or through the coronary sinus ostium. Alternatively, for simple cases such as repair of a secundum atrial septal defect, standard cannulation can be performed and a sump suction cathether placed into the coronary sinus while the right atrium is open.

## MASSIVE AIR EMBOLISM

Massive air embolism during perfusion is a rare but catastrophic event. When this is detected, perfusion should stop immediately and clamps should be placed on both venous and arterial lines. Air in the circuit should be removed rapidly by recirculation and entrapment of all air in a reservoir or bubble trap. The patient should immediately be placed in steep Trendelenburg and blood and air at the site of entry should be aspirated until no air is retrieved. TEE should rapidly be employed to search for air, but perfusion must resume promptly, depending on body temperature, to prevent ischemic brain damage. Cooling to deep hypothermia should be considered to protect the brain and other organs while the air is located and removed. As soon as possible, retrograde perfusion of the brain should be undertaken while the aortic arch is simultaneously aspirated with the patient in steep Trendelenburg. Corticosteroids and/or barbiturates may be considered. Depending on circumstances and availability, hyperbaric oxygen therapy may be helpful if patients can be treated within 5 h of operation.[34]

## DEEP HYPOTHERMIC CIRCULATORY ARREST

DHCA is used for operations involving the aortic arch, porcelain aorta, thoracoabdominal aneurysms, pulmonary thrombendarterectomy, selected uncommon cardiovascular and neurologic procedures, and certain complex congenital heart procedures. The technology involves reducing body temperature to less than 20°C, arresting the circulation for a short period and then rewarming to 37°C. Most surgical teams cool to either electroencephalographic (EEG) silence, jugular venous saturation above 95 percent, or for at least 30 min before stopping circulation at nasopharyngeal or tympanic membrane temperatures below 20°C. Perfusion cooling is usually supplemented by surface cooling using hypothermia blankets and/or packing the head in ice. During rewarming, hyperthermia is avoided by keeping the arterial inflow temperature below 37°C.

Changes in temperature affect acid–base balance, which must be monitored and managed during deep hypothermia. In adults, the pH-stat protocol ($CO_2$ is added to maintain temperature corrected blood pH at 7.4) is often used during cooling instead of the alpha-stat protocol, which allows cold blood to become alkalotic. Compared with alpha-stat, pH-stat increases the rate and uniformity of brain cooling and slows the rate of brain oxygen consumption by 30 to 40 percent. pH-stat is even more commonly used in pediatric DHCA applications. Alpha-stat management is often substituted during rewarming when more potential microemboli may be present. Hyperglycemia appears to increase brain injury and is avoided during deep hypothermia. The value of high-dose corticosteroids or barbiturates remains unproven.

The "safe" duration of circulatory arrest during deep hypothermia is unknown. In adults, arrest times as short as 25 min are associated with reduced performance on neuropsychologic tests of fine motor function and memory.[35] At 18°C, cerebral metabolism and oxygen consumption are 17 to 40 percent of normothermia, and abnormal EEG patterns and cerebrovascular responses can be detected after 30 min of circulatory arrest. Most investigators report increased mortality and adverse neurologic outcomes after 40 to 65 min of circulatory arrest. Thus, the maximal "safe" duration of DHCA is considered to be approximately 45 min by most surgeons. Advanced age or a preoperative history of stroke may leave less safety margin for brain injury.

Cerebral perfusion can often be maintained during DHCA in either antegrade or retrograde fashion. Interval resumption of normal circuit flow is ideal but is usually not technically possible except in cases not involving open work on the aortic arch, i.e., pulmonary thromboendarterectomy. Antegrade cerebral perfusion, which appears to have more clinical benefit than retrograde perfusion, is most easily applied after cannulation of the right axillary artery. The innominate artery can then be occluded to achieve corporeal circulatory arrest while maintaining flow to the brain via the right carotid artery. Flows usually range between 8 and 12 mL/kg to keep mean pressure in the range of 40 to 70 mm Hg in the right radial artery or pressure sensor on the end of the cannula. Less commonly, the cerebral vessels can be cannulated separately. Selective antegrade cerebral perfusion risks dislodging atheromatous emboli, air embolism, cerebral edema, or injury from excessive perfusion pressure.

Retrograde cerebral perfusion is achieved by placing a perfusion cannula (often a retrograde coronary sinus catheter) into the SVC, which is then perfused at flows between 250 and 400 mL/min and blood pressures usually between 25 and 40 mm Hg. A snare is usually placed around the SVC catheter cephalad to the azygos vein to reduce runoff. As minimal cortical perfusion has been detected with this technique, its main theoretical benefit is the retrograde flush of air and debris from the cerebral vessels. After increased use in the 1980s, retrograde cerebral perfusion was not widely employed because many studies had failed to demonstrate clinical benefit.

## CANNULATION FOR MINIMALLY INVASIVE SURGERY

Peripheral cannulation sites as described above may be used for minimal-access cardiac surgery, but often central cannulation of the aorta, atrium, or central veins is accomplished using specially designed or smaller cannulas placed through the small operative incision or through a separate small incision in the chest wall. Venous return is often augmented by applying negative pressure (see "Venous Cannulation," above). Specially designed cross clamps, some with flexible handles, can also be used through small incisions. Other options include complete cannulation by remote access, using equipment such as the Port Access System, which provides a means for full CPB, cardioplegia administration, and aortic cross clamping without exposing the heart and can be used for both valvular and coronary artery operations.[36] Separate transcutaneous catheters are inserted through the right internal jugular vein into the coronary sinus for retrograde cardioplegia and the pulmonary artery for left heart venting. A multilumen catheter is inserted through the femoral artery and, using TEE and/or fluoroscopy, is positioned in the ascending aorta for arterial pump inflow, for balloon occlusion of the ascending aorta, and for administration of antegrade cardioplegia into the aortic root. Venous return is captured by a femoral venous catheter advanced into the right atrium.

Minimally invasive surgery using CPB is associated with potential complications that include perforation of vessels or cardiac chambers, aortic dissection, incomplete de-airing, systemic air embolism, and failure of the balloon aortic clamp. As $CO_2$ is heavier than air and more soluble in blood, the surgical field is sometimes flooded with $CO_2$ at a flow of 5 to 10 L/min to displace air when the heart is open. The balloon clamp can leak, prolapse through the aortic valve, or move distally to occlude arch vessels. Early use of the balloon clamp appeared to be associated with higher risks of aortic dissection; with more experience, however, this complication appears less common. For safety, the position of the occluding balloon is closely monitored by TEE, bilateral radial arterial pressures, and occasionally transcranial Doppler ultrasound.

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## CARDIOPULMONARY BYPASS BOARD REVIEW QUESTIONS (CHAPTER 24)

1. Which surgeon pioneered "cross-circulation"?
   A. Gibbon
   B. Bigelow
   C. Lillehei
   D. Kirklin
   E. Mayo

2. Which of the following is not an advantage of a roller pump over a centrifugal pump?
   A. Reduced cost
   B. Minimal effects by afterload changes
   C. Low priming volume
   D. Generation of microparticles
   E. Ability to generate pulsatile flow

3. Which of the following is not an advantage of an open venous reservoir compared to a closed venous reservoir?
   A. Facilitation of volume measurements
   B. Easier to manage venous air
   C. Larger capacity
   D. Minimizes air–blood interface
   E. Reduced cost

4. Which is not an advantage of centrifugal cell-saving compared to cardiotomy suction?
   A. Removal of microparticles
   B. Reduced inflammatory response
   C. Lower incidence of neuropsychologic deficits
   D. Improved field clearance and visualization
   E. Reduced hemodilution

5. Which is true regarding alpha-stat management?
   A. pH of 7.40 at 28°C
   B. Increased cerebral blood flow
   C. Autoregulation of cerebral blood flow
   D. Increased administration of $CO_2$ during cooling
   E. Increased cerebral microembolization

## ANSWERS

1. **Answer: C.** Lillehei used cross-circulation to repair congenital defects prior to the advent of cardiopulmonary bypass. Bigelow utilized systemic hypothermia with topical cooling for early cardiac repairs. Gibbon was the first to clinically use the heart–lung machine, but it was Kirklin at the Mayo Clinic who ushered in the modern area of intracardiac surgery with modifications of the cardiopulmonary bypass circuit.
2. **Answer: D.** High negative pressures generated by a roller pump can cause cavitation and generation of microparticles. In general, roller pumps are less expensive and can function with lower priming volumes. There is minimal effect on the roller pump during afterload changes. The roller mechanism can be adjusted to generate pulsatile flow.
3. **Answer: D.** Open venous reservoirs have a larger air–blood interface and, therefore, may be associated with a higher risk of microgaseous emboli. Volume measurements and air management is easier with an open reservoir, which is larger and cheaper than a closed system.
4. **Answer: E.** Cell-saving with a centrifugal device has been shown to remove microparticles, reduce inflammation and neuropsychologic deficits, and improve operative visualization and field clearance. The disadvantage is the loss of plasma that occurs during the cell washing process.
5. **Answer: C.** Alpha-stat management is associated with better autoregulation of blood flow. It keeps the pH at 7.40 regardless of temperature, reduces cerebral blood flow according to autoregulation, and also reduces cerebral microembolization. pH-stat, not alpha-stat, management requires increased administration of $CO_2$ during cooling.

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# 25 Myocardial Protection

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**KEY CONCEPTS**

- Cardioplegia markedly reduces oxygen demand in the arrested heart and must be delivered uniformly in sufficient quantity to match this low demand.
- "Integrated myocardial protection" is a myocardial protection strategy that includes antegrade and retrograde delivery of cold-blood cardioplegia and warm cardioplegia perfusion for induction and resuscitation.
- Hypothermia reduces myocardial oxygen demand and ischemic injury when coronary flow is interrupted; however, it does not completely prevent injury in chronically ischemic hearts.
- Blood cardioplegia, which typically comprises four parts blood to one part crystalloid solution, is a natural buffering agent, maintains oncotic pressure, possesses advantageous rheologic properties, and is a free-radical scavenger.
- High potassium in cardioplegia maintains cardiac arrest and prevents sudden intracellular calcium accumulation and sarcolemma disruption.
- Complete myocardial recovery occurs after 4 h of ischemia in normal hearts when protected with cold-blood cardioplegia.
- Antegrade or retrograde delivery of cardioplegia alone does not provide homogeneous distribution even with normal coronary arteries.
- Paradoxical septal motion, seen in up to 40 percent of cardiac surgical patients, can lead to acute right ventricular failure and may be caused by inadequate distribution of cardioplegia.
- Warm-blood cardioplegia induction limits reperfusion injury in ischemic hearts.
- During antegrade infusion of cardioplegia, aortic pressure should be maintained between 60 and 80 mm Hg at a flow rate of 200 $cm^3$/min or, in hypertrophied hearts, at 250 $cm^3$/min.

## INTRODUCTION

A successful outcome after cardiac surgery depends on many factors. Accurate recognition of the pathology and the judicial choice of methods to achieve cardiac repair are essential. Equally important are the physiologic consequences of the operation. Ventricular function must be preserved or improved during cardiac procedures. Myocardial protection is therefore the crucial component of success in cardiac surgery.

The mainstay of myocardial protection is cardioplegia. This chapter is a brief review of myocardial protection as currently applied in the vast majority of cardiac operations worldwide. We offer a brief review of the components of cardioplegia and their effects on cardiac metabolism and function, followed by a detailed description of "how to do it."

Much has been written about cardioplegia regarding (1) route of delivery (antegrade vs retrograde or both), (2) method of delivery (continuous vs intermittent), and (3) temperature (warm vs cold). This has often led to confusion and adversarial positions. Surgeons appropriately want to keep things simple, but as Einstein once said: "Everything should be made as simple as possible, but not simpler." In this chapter, we present a method of cardioplegia that has been extensively applied clinically. It is called the "integrated method" of protection because it combines the salient features of the above elements in a manner that suits the ongoing physiologic needs of the heart during the course of an operation and expedites the time phase of the procedure.

## BASIS OF CARDIOPLEGIA

Cardioplegia markedly reduces oxygen demand in the arrested heart and must be delivered uniformly in sufficient quantity to match this low demand (Fig. 25-1). These

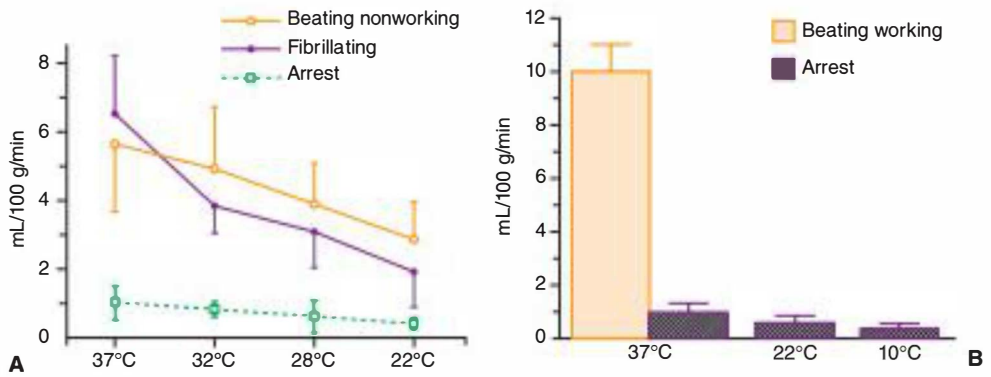



**FIGURE 25-1** Left ventricular (LV) oxygen requirements of the beating, empty, fibrillating, and arrested heart from 37°C to 22°C. Note in (**A**) the low oxygen demands of arrest and the negligible change between 22°C and 10°C as the heart rewarms from collateral flow. **B.** Higher demands exist if electromechanical activity returns when systemic perfusate washes out t he cardioplegic solution.

requirements are met by antegrade and retrograde delivery, cold-blood cardioplegia to reduce oxygen demands, and warm cardioplegia perfusion for induction and resuscitation. "Integrated myocardial protection" is a strategy that addresses each of these requirements in a manner that allows the operation to be performed without interruption.[1] This method (1) provides a bloodless operative field, (2) avoids unnecessary ischemia and cardioplegia overdose, and (3) permits aortic unclamping and discontinuation of bypass shortly after cardiac repair.

Electromechanical activity of the heart raises oxygen demand during arrest. Hypothermia reduces this demand and ischemic damage when coronary flow is interrupted in the course of the revascularization procedure provided that the cardioplegic perfusate is distributed adequately with reinfusions. Hypothermia alone, however, does not completely avoid injury in chronically "energy-depleted" (ischemic) hearts (Fig. 25-2).

## TYPES OF CARDIOPLEGIA

Blood cardioplegia consists of four parts of blood to one part crystalloid solution. It is a natural buffering agent, maintains oncotic pressure, has advantageous rheologic properties, and is a free-radical scavenger. Blood cardioplegia replenishes substrate in vulnerable hearts, limits reperfusion injury, and reverses ischemia/reperfusion changes in the acutely ischemic myocardium. Complete myocardial recovery occurs after 4 h of ischemia in normal hearts when protected with cold-blood cardioplegia. However, it is uncommon to address normal hearts. The sequences described below

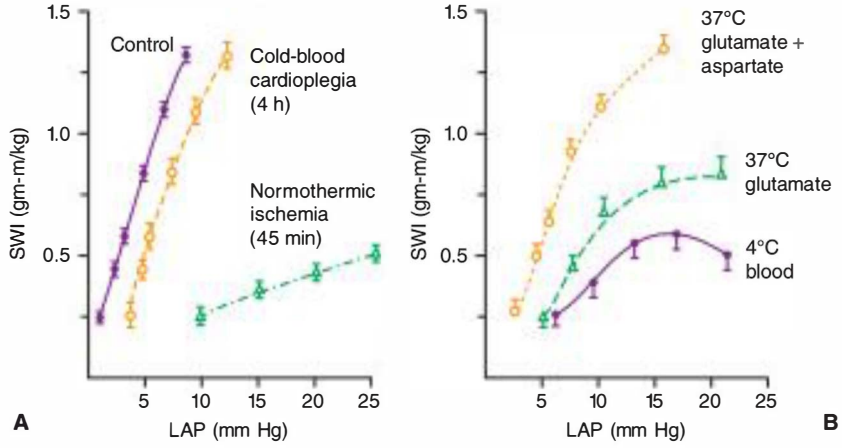



**FIGURE 25-2** **A**. LV function every 20 min in normal hearts subjected to 4 h of aortic clamping with blood cardioplegia compared with depressed function after 45 min of normothermic arrest without cardioplegia. **B**. LV function when jeopardized hearts undergoing 45 min of normothermic ischemia are subjected to 2 h more of aortic clamping. Note (1) no further improvement when only cold cardioplegic perfusate is given o ver the 45-min arrest period and (2) progressively increased recovery when the cardioplegic solution is supplemented with warm glutamate and aspartate during induction of cardioplegia and reperfusion with intermittent cold doses o f blood every 20 min of supplemental aortic clamping. These data suggest the value of amino acid enrichment in jeopardized hearts. LAP, left atrial pressure; SWI, stroke-work index.

**TABLE 25-1: Induction and Terminal "Hot Shot" Cardioplegia (Bag 1)**

| Cardioplegia additive | Volume added (mL) | Component modified | Concentration delivered[a] |
|---|---|---|---|
| Potassium chloride (2 mEq/mL) | 15 | Potassium ion | 16–20 mEq/L |
| Tromethamine (THAM) (0.3 mol/L) | 225 | pH | pH 7.5–7.7 |
| Citrate-phosphate-dextrose | 225 | Calcium ion | 0.2–0.4 mmol/L |
| Aspartate, glutamate | 250 | Substrate | 13 mmol/L each |
| 50% dextrose in water | 40 | Glucose | <400 mg/dL |
| 5% dextrose in water | 200 | Osmolarity | 380–400 mOsm |

[a]When mixed in a 4:1 ratio with blood.

were developed experimentally and are now clinically used routinely in the jeopardized hearts that are currently commonplace in cardiac surgical practice.

Cold-crystalloid cardioplegia does not have the rheologic advantages of blood cardioplegia. When administered in multiple doses, it often results in systemic hemodilution. Crystalloid cardioplegia also shifts the oxyhemoglobin disassociation curve leftward, retarding $Na^+/K^+$ adenosine triphosphatase, and thereby produces edema and activation of platelets, leukocytes, and complement.[2]

## COMPONENTS OF BLOOD CARDIOPLEGIA

Blood cardioplegia consists of four parts blood to one part crystalloid solution. The components (Table 25-1) of blood cardioplegia are reviewed briefly here and have been well described in detail previously.[3] Other more concentrated constituent dilutions (1:8 to 1:50) may be used if the crystalloid component is appropriately varied to include the components described in this chapter (Tables 25-2, 25-3, and 25-4).

A high level of potassium maintains cardiac arrest and prevents sudden intracellular calcium accumulation and disruption of the sarcolemma, as observed when reoxygenation occurs. A low level of calcium is used to limit calcium loading during the conditions of impaired ionic balance in the early period of reperfusion. The amino acid substrates aspartate and glutamate increase the energy-depleted heart's ability to use oxygen and hasten ionic recovery. Hyperosmolarity reduces edema. Tromethamine (THAM) is alkalotic to (1) limit the evolution of acidosis during ischemia and (2) hasten enzymatic recovery. It is used in preference to bicarbonate, which yields more $CO_2$ and acidosis.

We routinely use two formulations of cardioplegia (bags 1 and 2) during elective cardiac operations and switch between them based on the metabolic requirements of the heart during specific phases of the operation. Bag 1 is called "induction/terminal" cardioplegia and is a high-potassium (20 mEq/L), aspartate, and glutamate-enriched solution (Table 25-1). It is infused as a cold solution after aortic cross-clamping to arrest the heart and then infused as a warm solution just prior to the release of aortic cross-clamping after all cardiac repairs are completed to resuscitate the energy-depleted ischemic myocardium ("hot shot"). Bag 2 is called "maintenance" cardioplegia and consists of a low-potassium (7–10 mEq/L) mixture without the amino acid additives (Table 25-2). It is administered as a cold solution intermittently during the operation. A third cardioplegia (bag 3) is called "rescue" cardioplegia and is used following myocardial infarction as a controlled reperfusate (Table 25-3). Its rationale and use are described later in this chapter.

## DELIVERY OF CARDIOPLEGIA

Cardioplegia is effective only if it is well distributed. Adding retrograde perfusion via transatrial cannulation of the coronary sinus improves subendocardial perfusion, avoids

**TABLE 25-2: Cold Maintenance Cardioplegia (Bag 2)**

| Cardioplegia additive | Volume added (mL) | Component modified | Concentration delivered[a] |
|---|---|---|---|
| Potassium chloride (2 mEq/mL) | 10 | Potassium ion | 8–10 mEq/L |
| Tromethamine (THAM) (0.3 mol/L) | 200 | pH | pH 7.6–7.8 |
| Citrate-phosphate-dextrose | 50 | Calcium ion | 0.5–0.6 mmol/L |
| 5% dextrose in water 1/4 isotonic saline solution | 550 | Osmolarity | 340–360 mOsm |

[a]When mixed in a 4:1 ratio with blood.

**TABLE 25-3: "Rescue" Warm-Blood Cardioplegia Reperfusate[a] (Bag 3)**

| Cardioplegia additive | Volume added (mL) | Component modified | Final concentration |
|---|---|---|---|
| Potassium chloride (2 mEq/mL) | 40 | $K^+$ | 20–25 mEq/L |
| Tromethamine (THAM) (0.3 mol/L) | 225 | pH | 7.5–7.6 |
| Citrate-phosphate-dextrose | 225 | $Ca^+$ | 0.1–0.25 mmol/L |
| Glucose | 40$D_{50}$W | Glucose | >400 mg/dL |
| Osmolarity | — | Osmolarity | 380–400 mOsm |
| Glutamate | 125 | Substrate | 13 mmol/L |
| Aspartate | 125 | Substrate | 13 mmol/L |
| 5% dextrose and $H_2O$ | 250 | — | — |
| Diltiazem | 300 g/kg body weight | | |

[a]When mixed in a 4:1 ratio with blood.

ostial cannulation during aortic valve procedures, limits the removal of retractors during mitral procedures, and permits flushing of air and atheromas during coronary reoperations. Experimentally, right ventricular nutritive flow is limited by retrograde perfusion. Antegrade or retrograde cardioplegia alone are each inhomogeneous in their distribution in animals with normal coronary arteries as shown by microsphere studies. Therefore, both are needed to insure a uniform distribution in the myocardium.[4]

Clinical studies show that switching from antegrade to retrograde perfusion raises oxygen uptake and lactate washout, indicating that each modality perfuses different areas.[5] Therefore, both antegrade and retrograde perfusion is required for complete protection (Fig. 25-3). The clinical benefits of the addition retrograde cardioplegia after coronary surgery were seen in a controlled prospective randomized trial. Three months after surgery, there was an increase in resting and exercise ejection fraction in patients who had retrograde cardioplegia as compared to those who did not.[6] Adding retrograde to antegrade cardioplegia also reduces troponin levels after induced ischemia in patients with reduced ejection fraction less than 36 percent.[7,8] In patients with left-main coronary disease, adding retrograde cardioplegia during coronary bypass reduces the incidence of postoperative atrial fibrillation and troponin levels.[9]

Recent studies have shown that combined benefits occur by *simultaneous* delivery of retrograde and antegrade cardioplegia in coronary bypass procedures.[10,11] After vein grafting to a coronary artery, cardioplegia may be given through the graft in an antegrade manner and simultaneously through the coronary sinus. Myocardial venous hypertension is prevented by drainage through the Thebesian veins.

Noncoronary collateral flow from mediastinal collaterals displaces cardioplegia with warmer systemic blood. Topical hypothermia slows rewarming but may cause pulmonary complications (phrenic palsy) without supplementing the cardioprotective effects. Hence, continuous or intermittent cardioplegia is required. Continuous cardioplegic perfusion has been advocated to avoid ischemia, but adequate protection may not be achieved at usual flow rates, and the surgeon's vision becomes obscured during infusion. Intermittent cardioplegia, delivered at 10- to 20-min intervals, maintains arrest, slows rewarming, and restores substrates depleted during ischemia. In addition, it flushes accumulated metabolites and counteracts acidosis and edema.

## SEPTAL FUNCTION AND CARDIOPLEGIA

Paradoxical septal motion, seen in as many as 40 percent of patients after cardiac surgery can lead to acute right ventricular failure.[12] This may be caused by inadequate distribution of cardioplegia. We recently evaluated septal function

**TABLE 25-4: Modified Noncardioplegic Cold Blood (Bag 4)**

| Solution additive | Volume added (mL) | Component modified | Concentration delivered[a] |
|---|---|---|---|
| Tromethamine (THAM) (0.3 mol/L) | 50 | pH | pH 7.5–7.6 |
| Citrate-phosphate-dextrose | 50 | Calcium ion | 0.5–0.6 mmol/L |
| Magnesium chloride (2 mEq/mL) | 10 | Magnesium ion | 4–6 mg/L |
| 5% dextrose in water 1/4 isotonic saline solution | 1000 | Osmolarity, glucose | 340–360 mOsm |
| Mannitol (25%) | 50 | Osmolarity, oxygen-radical scavenger | 340–360 mOsm |

[a]When mixed in a 4:1 ratio with blood.

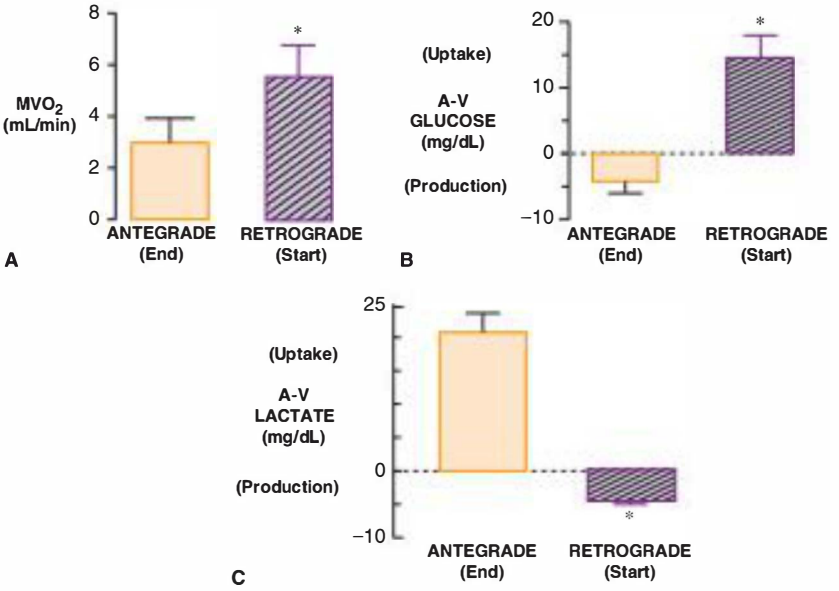



**FIGURE 25-3** Myocardial metabolic changes in coronary patients when cardioplegic induction solution is converted from antegrade to retrograde. Note the increase in myocardial oxygen uptake ($MVO_2$), glucose uptake, and lactate production, suggesting different areas of perfusion by the antegrade and retrograde methods of delivery. This implies an advantage to both methods.

by a commonly used qualitative scoring system and reported septal function among 119 patients undergoing a variety of cardiac surgical procedures.[13] By using the integrated method of myocardial protection, paradoxical septal motion was not seen in any patient, strongly suggesting that this phenomenon is an iatrogenic injury or stunning of the septum. A prospective randomized clinical trial is currently underway with newer echocardiographic data including spectral tracking and velocity vectors.

## TEMPERATURE OF CARDIOPLEGIA

Integrated myocardial management also addresses the special needs of the myocardium based on nutritive needs and underlying pathology. Hence, both cold and warm cardioplegia is used in this method at various times.

During routine elective operations in patients with good ventricular function, cardioplegic arrest is done with cold-blood cardioplegia (bag 1). If ventricular function is impaired or there is active ischemia, induction is carried out with warm cardioplegia (bag 1). In both cases, cardioplegia is first given antegrade and then retrograde. If the heart is arrested with a warm induction, low-potassium nonenriched cardioplegia (bag 2) is then given antegrade and retrograde to cool the heart. Temperature is always monitored in the septum to assure optimal cooling and distribution.

Warm-blood cardioplegia (37°C) given initially (induction) limits reperfusion damage in ischemic hearts.[14] It enhances metabolic repair by channeling aerobic adenosine triphosphate production to reparative processes. Other cardioplegic components, citrate–phosphate–dextrose (CPD), and buffers (THAM) limit calcium influx and acidosis. Clinical studies confirm our experimental findings and show that warm-blood cardioplegia ("hot shot") after ischemia improves recovery. Warm cardioplegic induction and reperfusion solutions are augmented with the amino acids glutamate and aspartate to replenish key Krebs cycle intermediates depleted by ischemia. These additions enhance the reparative processes after a period of myocardial ischemia. The use of warm induction and reperfusion has been shown to decrease troponin levels after a period of ischemia clinically.[15] A modified warm cardioplegia known as "rescue" cardioplegia may be used to resuscitate the arrested heart after acute myocardial infarction or cardiac arrest occurring soon after bypass surgery.[16] The solution (bag 3, Table 25-3) contains the amino acid–enriched solutions with the addition of diltiazem, which limits calcium influx into the injured myocardium. This solution may be infused for 20 min selectively into the infarcted artery via a saphenous vein bypass prior to its attachment to the aorta. During this phase, the ventricle is vented via the right superior pulmonary vein. Rescue cardioplegia may also be used globally (antegrade and retrograde, alternating 5 min each for 20 min). We have observed marked rhythm and hemodynamic improvement after witnessed cardiac arrest of up to 120 min with this approach.

## AORTIC CLAMPING

Coronary artery bypass grafting (CABG) is the most common cardiac operation, and the risk of intraoperative cerebral atheroemboli is increased among elderly patients undergoing revascularization. Atherosclerotic emboli are more

likely after repeated aortic tangential clamping for proximal anastomoses. The integrated approach of myocardial protection permits bypass grafting and all cardiac procedures to be performed with single clamping of the aorta. The use of single-aortic cross-clamping has been avoided by some owing to concern that this method will extend the ischemic time. There is evidence that morbidity and cost are reduced despite a longer aortic clamp time when integrated protection is applied.[17] These findings contradict the notion that surgeons must battle the clock when the aorta is clamped. The extent of cardiac damage is related to *how* the heart is protected rather than *how long* the aorta is clamped. Blood cardioplegia provides sufficient cardiac nourishment during aortic clamping to permit excellent myocardial protection.

## CARDIOPLEGIC TECHNIQUE

This is a general overview of how cardioplegia is used in typical operations. Special situations and details pertaining to specific operations are further reviewed.

Cardiopulmonary bypass is initiated with core cooling to about 34°C. The aorta is clamped and cold bag 1 is infused antegrade at a flow of 300 mL/min over a 2-min period. The cold bag 1 is then infused via a retrograde cannula into the coronary sinus at a flow of 200 mL/min for 2 min. Septal temperature is monitored throughout. A temperature below 14°C indicates good distribution of cardioplegia and adequate cooling. All cardiac repairs are done while the aorta is clamped, including proximal anastomosis. Intermittent maintenance cardioplegia, bag 2, is given at 15-min intervals, both antegrade and retrograde. After cardiac repairs are completed, a warm reperfusate ("hot shot") is infused antegrade for 2 min (150 mL/min) and then retrograde (150 mL/min). This is followed by a continuous infusion of warm noncardioplegic blood antegrade into the aortic root while the cross-clamp is still in place at a flow of 300 to 350 mL/min at a pressure equal to or less than 80 mm Hg. The aortic clamp is released usually within 3 to 5 min after adequate contractility is observed. The aortic vent is activated and the patient tilted with the head slightly down to evacuate any air while the heart is ejecting.

Alternatively, bag 1 ("warm induction") is used initially to arrest the heart where acute ischemia is present or in cases of severely depressed systolic function. The administration of substrates in this situation has been proven to improve postoperative function. After the warm induction, bag 2 maintenance cold-blood cardioplegia is infused antegrade and retrograde as above.

## CARDIOPLEGIA DELIVERY SYSTEMS

All operations include the use of a heat exchanger to cool or warm the cardioplegia (Fig. 25-4), cannulas for antegrade and retrograde delivery, and a monitoring-infusion system. The system we use is shown in Figure 25-5. The three controls are color-coded and easily within reach.

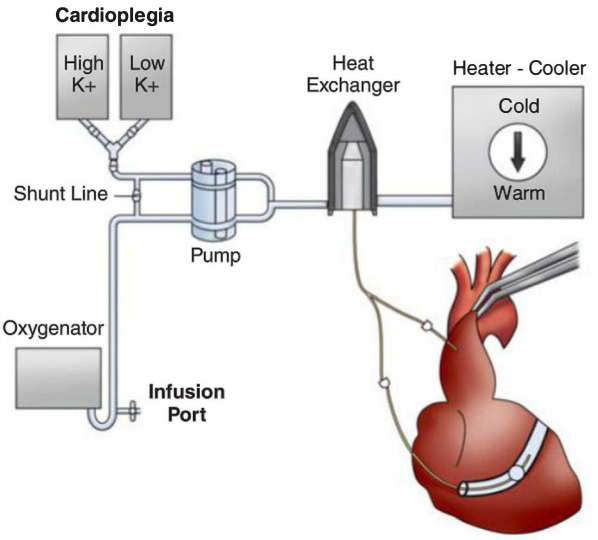



**FIGURE 25-4** Blood cardioplegic delivery system for high-dose (bag 1) and low-dose (bag 2) cardioplegia solutions. These are mixed 4:1 with blood from the oxygenator. The shunt line allows delivery of blood through the roller head of the pump after the warm reperfusate is given.

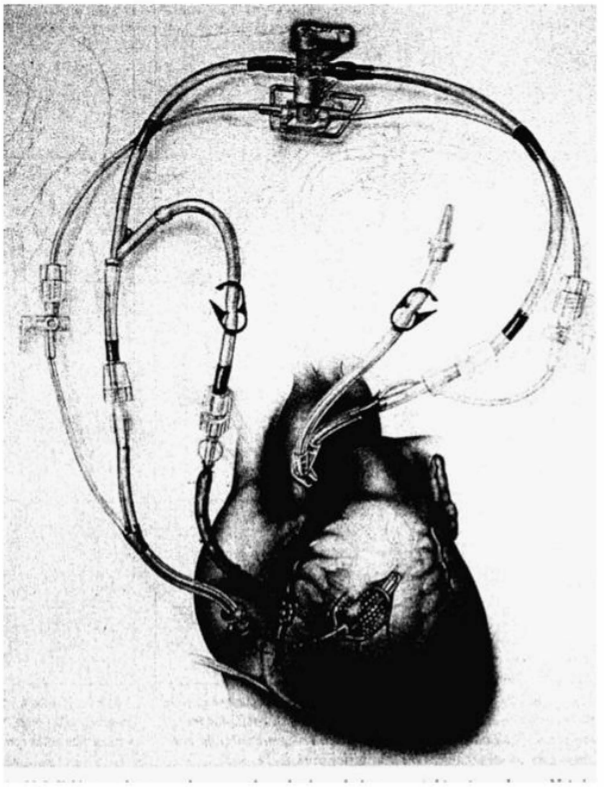


**FIGURE 25-5** Tubing use for antegrade, retrograde, and vein perfusion connected to the retrograde arm. Note the stopcock that allows simultaneous delivery of cardioplegic perfusate and monitoring of arterial or coronary sinus pressure. The tubing connected to the retrograde limb allows simultaneous retrograde/antegrade perfusion down the vein graft or right coronary ostium during aortic valve replacement.

1. A stopcock that switches between antegrade and retrograde infusion. Attached to these infusion lines are thinner ones for infusion-pressure monitoring.
2. A flow clamp to activate the aortic vent.
3. Flow clamps on the retrograde line and on a line attached to this line. The latter can be used to deliver cardioplegia through a vein graft or directly into the coronary ostia via a handheld cannula during aortic valve operations (Fig. 25-5).

An *antegrade* cannula is placed high in the right ascending aorta and slightly to the right side. This cannula contains a pressure line and a vent port to suction air and blood between infusions. Since we use a single-aortic clamping for all operations, when proximal grafting of vein is performed, blood can be vented from the aorta while giving continuous retrograde cold noncardioplegia blood. Placing this cannula slightly to the side of the aorta away from the anterior surface allows pooled blood to be effectively suctioned, thereby permitting good visualization of the anterior surface of the aorta for grafting. This site is not used for proximal grafting and is secured with a purse-string suture at the end of the operation.

The *retrograde* cannula has a self-inflating or manually inflated balloon at its tip; it also contains a line for monitoring infusion pressure. It is placed low in the right atrium, anterior to the venous cannula, and just above the caval junction. It is directed into the coronary sinus by aiming at the left shoulder. The cannula is advanced until it meets resistance within the coronary sinus, usually adjacent to the left atrial appendage (Figs. 25-6 and 25-7).

The coronary sinus can be injured by forceful cannulation or continued administration of cardioplegia when coronary sinus pressure exceeds 50 mm Hg. This can occur while the heart is elevated during circumflex artery grafting. The perfusionist notes high pressure, then low pressure as a consequence of acute perforation, or the surgeon sees red blood accumulate in the pericardial well. Perforation can be repaired directly with 5-0 polypropylene sutures or pericardial pledgets if the tear site is not distinct. Hematomas are often self-contained after heparin reversal.

## MONITORING CARDIOPLEGIA LINE PRESSURE

The regulation of cardioplegia infusion pressure avoids edema and endothelial damage. It also detects aortic insufficiency produced by distortion of the noncoronary aortic cusp by the venous cannula or clinically insignificant regurgitation. Slight manual compression of the right ventricular outflow tract will push the septum against the posterior left ventricle and close the aortic valve, allowing adequate root pressure. During retrograde infusion, measurement of pressure verifies correct placement of the coronary sinus cannula.

During antegrade infusion, aortic root pressure is maintained between 60 and 80 mm Hg at a flow rate of 200 mL/min or, in hypertrophied hearts, 250 mL/min. Blood cardioplegia is given over time to ensure maximal oxygen delivery. Failure

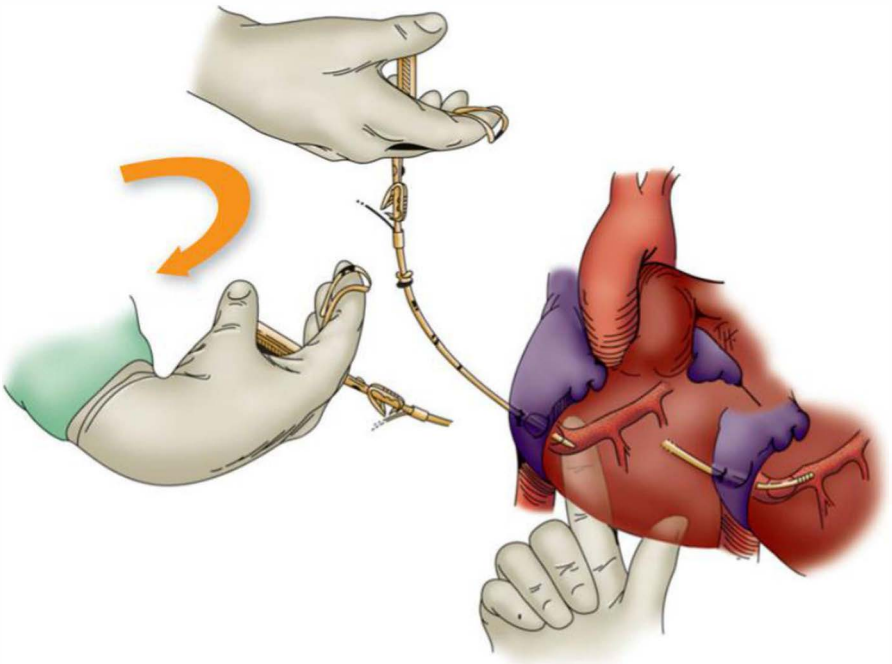


**FIGURE 25-6** Method for introducing the retrograde cannula. Note that the cannula is rotated anteriorly and toward the left shoulder to follow the course of the coronary sinus.

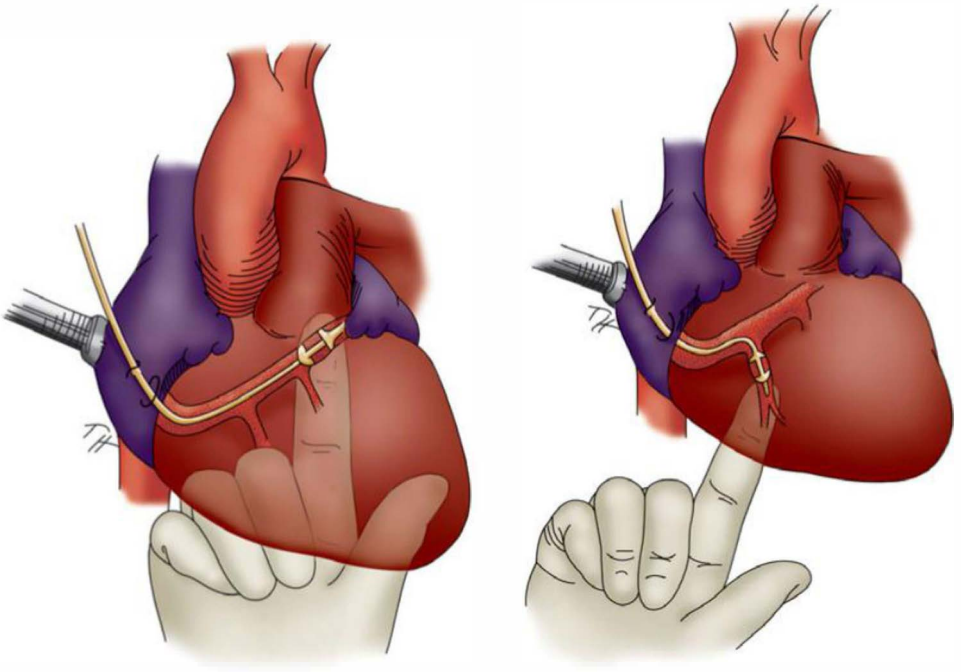



**FIGURE 25-7** **A.** Correct placement of retrograde catheter. **B.** Incorrect placement of catheter into coronary vein, confirmed by palpation.

to arrest means inadequate systemic venous drainage (full heart), incomplete aortic clamping, or aortic insufficiency. Aortic pressure of below 30 mm Hg means that antegrade flow is insufficient and only retrograde infusion should be used. High aortic pressure (greater than 100 mm Hg) may occur with extensive obstructive coronary disease. If this happens, the infusion rate should be slowed to give the correct dose over time. During the final warm cardioplegia infusion ("hot shot"), the aortic root pressure should not exceed 50 mm Hg to avoid endothelial dysfunction.

During retrograde infusion, coronary sinus pressure is maintained between 20 and 40 mm Hg at a flow of 200 mL/min. A coronary sinus pressure greater than 50 mm Hg means improper positioning or cardiac retraction. This is corrected by reducing the flow rate immediately, repositioning the catheter, and then resuming the flow. Textured balloons should not be moved during infusion because of coronary sinus wall traction and possible injury. A coronary sinus pressure below 20 mm Hg indicates that the balloon is not inflated or not occluding the coronary sinus. The cannula tip and balloon should then be repositioned by palpation. Added maneuvers to improve retroperfusion include compressing the junction of the coronary sinus and right atrium or placing a snared suture around the coronary sinus, thus, fixing it in place and preventing regurgitation of cardioplegia into the atrium. Other rarer causes of low pressure include persistent left superior vena cava (SVC) and left atrial unroofing of the coronary sinus. The presence of a left SVC is usually determined before cardiopulmonary bypass and the vessel occluded with a tourniquet only if an intact innominate vein is present. If the innominate vein is absent, only antegrade cardioplegia is used to avoid myocardial underperfusion.

## APPLICATIONS OF CARDIOPLEGIA

### Coronary Artery Bypass Grafting

During CABG operations, the body is cooled to 34°C. The heart is arrested with high-potassium *cold*-blood cardioplegia (bag 1) in elective low-risk operations with good ventricular function. For simplicity, this solution is enriched with aspartate and glutamate, rather than preparing another solution without these. Cardioplegia is delivered antegrade (300 mL/min for 2 min), then retrograde (200 mL/min for 2 min). Alternatively, this same potassium-enriched *warm*-blood cardioplegia ("warm induction") is used initially to arrest the heart in cases of acute ischemia or severely depressed systolic function. After the warm induction, maintenance low-potassium cold-blood cardioplegia (bag 2) is infused into the aortic root and retrograde into the coronary sinus. This same solution is used intermittently during the course of the grafting.

Following cardioplegic arrest, all anastomoses are constructed in a dry operative field using distal/proximal grafting in sequence. The right coronary is grafted first because retrograde nutritive perfusion is limited. Maintenance

cardioplegia (bag 2) is then given retrograde simultaneously via the coronary sinus cannula and its side-arm antegrade into the newly grafted vessel at a flow rate of 200 mL/min for 1 min. Air is purged from the graft as the distal coronary suture is tied. This maneuver protects the right ventricle by antegrade direct coronary perfusion. The left ventricle is simultaneously protected by retrograde perfusion. The aortic vent is temporarily closed to distend the aortic root. While cardioplegia is infusing retrograde and simultaneously through the unattached vein graft, determination of graft length in the distended vein becomes quite easy.

During proximal grafting of vein to the aorta, retrograde cold noncardioplegic blood is infused at 200 mL/min. Cold blood maintains arrest and limits potassium overdose. This solution can be enhanced with CPD, THAM, magnesium, and mannitol, which prevent resumption of low-level electromechanical activity (bag 4, Table 25-4). The aorta is vented by active suction during proximal grafting, allowing good visualization. When proximal grafting is completed, cardioplegia infusion is then switched to the antegrade mode. Air is evacuated from the aortic root as the proximal suture line is secured. Air is also evacuated from the grafts during antegrade infusion with a 27-gauge needle.

Newly constructed grafts perfuse the heart after each proximal connection. The next distal graft is then constructed in a dry operative field while the heart is vented. The sequence is repeated for each distal and proximal anastomosis, leaving one proximal graft to be connected to the aorta after the final distal left internal mammary artery (LIMA) anastomosis is constructed. While the LIMA anastomosis is begun, systemic rewarming is started and the cardioplegic solution is rewarmed.

After the LIMA is grafted, antegrade warm enriched cardioplegia (bag 1) is delivered for 2 min at a flow of 150 mL/min, followed by retrograde warm cardioplegia, also at a flow of 150 mL/min. During the retrograde infusion, the last proximal vein graft is sewn to the aorta, followed immediately by infusion of warm noncardioplegia blood at a flow of 250 to 300 mL/min until the proximal grafting is complete. The heart usually begins contracting and systolic compression of the capillary bed raises coronary sinus pressures, but this is of no concern. Antegrade flow is started to de-air the aortic root, as before, and the grafts are de-aired with the 27-gauge needle to prevent air embolus.

## Combined Operations

In combined valve/coronary procedures, distal coronary grafting is performed first. The valve is then replaced or repaired. Every 15 to 20 min, maintenance cold cardioplegia (bag 2) is delivered through the unattached vein grafts and simultaneously into the coronary sinus. All proximal anastomoses are then constructed while the aorta is clamped. The proximal right graft is sewn last to maximize right ventricular perfusion. Warm cardioplegic reperfusion (bag 1, "hot shot") is started at the end of the next to the last proximal anastomosis. The perfusionist then delivers retrograde warm blood and the aorta is vented gently while the final right graft is sewn to the aorta. As the high-potassium cardioplegia is washed out, the heart begins contracting slowly. The stopcock is switched to antegrade infusion of warm blood as described earlier. When good contractility is observed, the aortic clamp is removed and the patient weaned from cardiopulmonary bypass, usually with minimal inotropic support. Phenylephrine infusion at 0 to 2 μg/kg/min is often needed, since the enriched solutions tend to cause a transient mild vasodilation.

## Evolving Myocardial Infarction

The procedure is slightly modified for patients with acute evolving myocardial infarction and total occlusion of a coronary artery. Cardiopulmonary bypass is instituted in the usual manner with systemic cooling to 34°C. The left ventricle is vented via the right superior pulmonary vein to minimize myocardial oxygen demands. The aorta is clamped and the heart arrested with a warm induction (bag 1), as previously described, followed by maintenance cold cardioplegia (bag 2). The noninfarct vessels are grafted first, as described previously for treating high-risk coronary patients. All proximal anastomoses are made except for one graft, which will be connected to the aorta during the 20-min interval for infarct vessel reperfusion described below. The whole heart receives a final "hot shot" cardioplegia, followed by retrograde warm-blood infusion as in the standard CABG operation.

Following completion of distal and proximal grafting of the compensating remote muscle (except one graft to remote noninfracted muscle), the infarct-related artery is grafted last, following perfusion with warm "rescue cardioplegia" (bag 3) at 50 mL/min (≤50 mm Hg pressure) for 20 min (Table 25-3). This is a substrate-enriched, hyperosmotic, hypocalcemic, alkalotic, and diltiazem-containing solution. Connection of the last proximal graft going to remote muscle is made during prolonged infarct graft perfusion. This interval allows ongoing surgical activity during this 20-min warm infusion via the infarct vessel.

The last proximal anastomosis (from the infarct region) is made after the prolonged reperfusion via the infarct graft. Warm retrograde normal blood perfusion is distributed to the infarct region during this interval of making the aortic connection so as to avoid additional ischemia. Cardiopulmonary bypass with the vented heart is continued for 30 min more, to allow recovery of the newly revascularized infarcted myocardium. We have observed significant return of regional contractility despite more than 6 h of ischemia. The details and outcome of this technique have been previously described.[8]

## Cardiac Reoperations

The integrated cardioplegia method described above has been found to be particularly useful in repeat operations. In

coronary bypass operations, a generally accepted rule is that old grafts should be left undisturbed. This "no touch" technique prevents embolization of friable atherosclerotic debris into the distal vasculature.

Following sternotomy, only the aorta and right atrium are dissected free of surrounding adhesions. Following cannulation and institution of cardiopulmonary bypass, cardioplegia is delivered as in no repeat operations. The aorta is vented to decompress the heart, and only then is the heart freed of surrounding pericardial adhesions. This avoids compression of old vein grafts and remobilization. Distal and proximal grafts are constructed in sequence, as with all coronary operations. The single-aortic cross-clamping technique avoids compression of old grafts and ischemia, which can be induced by the side-biting aortic clamping method, where graft flow is temporarily interrupted.

Clinical outcomes with this method in repeat CABG have demonstrated no increased mortality, even in patients with markedly reduced systolic function preoperatively.[18]

## Myocardial Protection During Aortic Root Replacement

The myocardium must be carefully protected during repair of ascending aortic aneurysm or dissection. The coronary ostia are often isolated for reimplantation into a graft. Intermittent cardioplegia can be administered directly into the unattached ostia, but care must be taken to avoid injury, particularly in cases of aortic dissection. An approach we have found useful is to first graft the right coronary artery with saphenous vein. The proximal right coronary artery is temporarily occluded with a Silastic vascular loop. Cardioplegia can then be administered intermittently antegrade via the right coronary artery and simultaneously retrograde into the coronary sinus. This permits maximum distribution throughout the myocardium and does not interfere with the operation. The aortic root and ascending aorta can be repaired with ease in a dry field. After the root has been reconstructed, the ostia are reimplanted into the graft and the saphenous vein graft ligated at the anastomosis to the right coronary artery, with either a running suture or a large clip. This method assures global myocardial protection and avoids injury to the friable coronary ostia.

## CONCLUSIONS

"Integrated myocardial management" as described above allows cardiac procedures to proceed smoothly and rapidly, since there is no interruption or delay for infusion of cardioplegia. The duration of cardiopulmonary bypass is actually shortened while simultaneously taking advantage of the benefits of different methods. Ongoing studies will likely lead to the incorporation of additional cardioprotective methods, such as preconditioning agents, white blood cell filters, oxygen-radical scavengers, endothelium-enhancing agents, and molecular factors, which will further improve the safety of ischemic intervals and limit reperfusion damage.

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## MYOCARDIAL PROTECTION BOARD REVIEW QUESTIONS (CHAPTER 25)

1. Which of the following is not a basic requirement of cardioplegic arrest?
   A. Creation of a dry, bloodless field
   B. Cessation of electromechanical activity
   C. Reduction of myocardial oxygen demand
   D. Retrograde cardioplegia
   E. Uniform delivery of cardioplegia

2. Which of the following is correct regarding blood cardioplegia?
   A. Only method available for cardiac arrest
   B. Allows complete recovery of function after 4 h of arrest
   C. Can only be used in anticipated arrest time is under 2 h
   D. Shifts the oxyhemoglobin dissociation curve to the left
   E. Must ideally be given cold

3. Which is correct regarding the composition of blood cardioplegia?
   A. Has high levels of calcium added to improve contractility
   B. Is hypoosmolar
   C. May contain amino acid substrates to hasten recovery
   D. Has low levels of potassium to prevent systemic hyperkalemia
   E. Typically consists of one part blood and one part crystalloid

4. Which of the following is true for retrograde cardioplegia?
   A. Perfuses the same areas as antegrade cardioplegia
   B. Is cumbersome and technically demanding
   C. Often requires bicaval cannulation and insertion of the catheter under direct vision
   D. Can be given simultaneously with antegrade cardioplegia
   E. Has no proven clinical benefit

5. Which is correct regarding delivery techniques for cardioplegia?
   A. Adequacy of delivery can be determined by manual palpation of the aorta or coronary sinus
   B. Adequacy of delivery can be monitored by the perfusion line pressure
   C. Retrograde infusion pressures above 50 mm Hg require repositioning of the retrograde catheter
   D. If the aortic root pressure exceeds 100 mm Hg during antegrade delivery, retrograde cardioplegia should be initiated
   E. Adequacy of delivery can be monitored by direct measurement of pressure in the delivery catheter

## ANSWERS

1. **Answer: D.** Delivery mode is not a basic requirement of cardioplegia. Antegrade, retrograde, and combination delivery have all been shown to be effective. Creation of a dry, motionless, and bloodless field provides the surgeon optimal working conditions. The cardioplegia should reduce myocardial oxygen demand and be uniformly delivered to all regions of the heart for protection.
2. **Answer: B.** Experimental and clinical outcomes have shown excellent recovery of myocardial function even after several hours of arrest using blood cardioplegia. It can be delivered at a variety of temperatures and is suitable even for short arrest periods.
3. **Answer: C.** A wide range of additives have been proposed for blood cardioplegia. The amino acid substrates aspartate and glutamate have been experimentally shown to become depleted during cardiac arrest. Addition of these substrates results in a more complete recovery of myocardial function.
4. **Answer: D.** Simultaneous antegrade and retrograde cardioplegia can be accomplished because there is adequate drainage through Thebesian veins. Another approach is simultaneous retrograde coronary sinus cardioplegia and antegrade delivery down a vein graft. Retrograde cardioplegia can be associated with decreased perfusion of the right heart. It is simple and is typically easily accomplished with blind insertion of the catheter into the coronary sinus. It has particular benefit in patients with active ischemia and high-grade coronary artery disease.
5. **Answer: C.** A pressure exceeding 50 mm Hg during retrograde cardioplegia indicates that the catheter has advanced too far and there is risk of coronary sinus rupture. High antegrade pressures do not require switching to retrograde cardioplegia but rather signal high-grade coronary artery disease. Adequacy of delivery is not determined by pressure measurements.

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26

# Postoperative Management of the Cardiac Surgical Patient

*Rashna Ginwalla*
*Nauder Faraday*
*Glenn Whitman*

**KEY CONCEPTS**

- Cardiac surgery involves unique anatomic and physiologic stresses that tax the reserve of every organ system. Continuous postoperative surveillance is required for early recognition of pathology and for rapid institution of organ and life-preserving therapies.
- Cardiac surgery causes transient (lasting 12–24 h) myocardial injury, sympathetic hyperreactivity, and the systemic inflammatory response syndrome (SIRS) in nearly all patients. As a result, hemodynamic instability requiring transient pressor and/or vasodilator infusions and intravascular volume expansion should be expected in all patents during the first 6 to 24 postoperative hours.
- Atrial fibrillation/flutter occurs in 30 percent of patients after cardiac surgery, and its incidence can be reduced by half through prophylactic administration of β-blockers, amiodarone, or sotalol.
- Significant pulmonary compromise should be expected in all cardiac surgical patients postoperatively, with 5 percent of patients experiencing overt respiratory failure. Diuresis should be instituted as soon as SIRS abates to limit fluid accumulation in the injured post-CPB lung.
- Liberation from mechanical ventilation should be sought at the earliest possible time in all patients. Extubation in most patients can be achieved as soon as they are awake enough to maintain airway patency and achieve adequate spontaneous gas exchange. In patients with significant respiratory compromise, daily assessment of a spontaneous breathing trial is the best method to assess readiness for extubation.
- Aggressive glucose control with a goal of 100 to 140 mg/dL within 24 h of ICU arrival reduces the incidence of death, sepsis, and renal failure after cardiac surgery.

## INTRODUCTION

Over the past 20 years, the cardiac surgery patient has become more acute, with sicker patients being operated upon. As an example, at Johns Hopkins, just in the past several years, the portion of elective cases for coronary artery disease (CAD) has decreased from 75 percent to approximately 40 percent, while urgent cases have increased from 25 percent to over 50 percent. Nevertheless, despite this increase in acuity of disease, the expected mortality for this same population has remained constant, at approximately 2 percent. It is more than possible that these similar outcomes in the face of sicker patients are the result of improvements in intra- and postoperative management strategies. It goes without saying that prevention of complications requires a thorough understanding of the pathophysiologic basis for the development of organ dysfunction after cardiac surgery, the ability to identify high-risk patients, and the ability to execute therapeutic strategies that prevent complications from developing. In many of those patients who develop complications, early diagnosis and treatment prevent further deterioration and limit subsequent morbidity and mortality.

The early management of the postoperative open heart surgery patient can be viewed as an extension of the intraoperative care the patient received, with a focus on recovery from hypothermia, restoring hemostatic capability, recognition and support during the inflammatory condition

provoked by cardiopulmonary bypass (CPB) itself, and optimization of cardiac function as the heart recovers from the transient ischemic injury sustained while undergoing surgery. Our experience at Johns Hopkins suggests that roughly one-half of all open heart surgery patients have recovered sufficiently to be transferred out of the ICU to the step-down unit in a day and a half, and that for isolated coronary bypass procedures, the ICU recovery period lasts for less than 1 day. Nevertheless, 30 percent of patients remain in the ICU for more than 3 days, and more than 10 percent stay for more than 7 days, indicating that in those patients, at a time when the immediate recovery from intraoperative events peculiar to CPB should have been long over, persistent organ dysfunction requiring critical care continues. To a large degree, the disease processes associated with this latter group of patients are similar to those seen in noncardiac surgical intensive care. Nevertheless, whether in the acute recovery period or a more chronic phase of critical illness, effective postoperative management rests on early recognition of pathology and rapid institution of therapy to prevent further clinical deterioration or the development of overt morbidity. This chapter is designed to review those physiologic disturbances specifically related to postoperative cardiac surgery patients as well as the more common illnesses and conditions associated with critical care, in general.

## PATHOPHYSIOLOGY OF ORGAN DYSFUNCTION AFTER CARDIAC SURGERY

Cardiac surgery involves a number of unique anatomic and physiologic stresses that tax the reserve of every organ system and increase the likelihood that clinical morbidity will develop. A list of these stressors and their pathophysiologic and clinical sequelae is shown in Table 26-1.

## GENERAL MANAGEMENT ISSUES IN THE EARLY POSTOPERATIVE PERIOD

The early postoperative period is characterized by instability involving vascular tone, significant fluid shifts, pulmonary and cardiac function, hemostasis, and renal function. This instability is a direct result of the anatomic and physiologic disturbances that take place intraoperatively (see Table 26-1). In general, resolution is rapid because the primary stressors causing instability (i.e., insults related to CPB) are confined to the first 12 to 24 h postoperatively. Once removed from these intraoperative influences, patients recover rapidly, so long as organ systems were not hurt in a more severe fashion and that the insult of CPB was not too severe for the organ systems that may already have been dysfunctional. Intensive monitoring is needed during this initial recovery phase to determine if the patient has deviated beyond what one normally expects during this critical postoperative time period.

### Transfer of Care and Monitoring

Transport of the patient and the transfer of care from the OR to the ICU is an inherently dangerous process. To reduce risk, hemodynamic stability should be assured prior to leaving the OR. Monitoring during transfer should be at a level comparable to that used intraoperatively and should include at a minimum the following: electrocardiogram (ECG), arterial blood pressure (BP), and pulse oximetry.

On arrival in the ICU, all care providers should initially focus on assuring the adequacy of cardiopulmonary function. Although the anesthesia team who knows the patient well should provide guidance to the receiving care team, in general, mechanical ventilation is protocolized, for example, tidal volume set at 7 to 8 $cm^3$/kg ideal body weight with a rate of 16, a positive end expiratory pressure set at 5 $cm^3$ $H_2O$, and the $FIO_2$ at 1.0. At that point, successive blood gases dictate changes required in ventilation while the weaning of $FIO_2$ can be guided by the $SpO_2$. It should be noted that shivering in response to hypothermia increases $O_2$ consumption and $CO_2$ production, thus increasing the workload of the pulmonary system. As a sedated, postoperative patient may not produce adequate respiratory compensation for this increase in work, hypercapnia with significant respiratory acidosis may ensue unless mechanical ventilation is maintained at appropriate levels.

Hemodynamic monitoring should be reestablished at the intraoperative level. All patients should have arterial BP monitoring. In addition, continual ECG monitoring with ST-segment analysis is standard so as to allow for the early detection of arrhythmias and ischemia. The combination of leads allowing the most sensitive detection of ischemia is somewhat controversial. Some authors advocate monitoring leads $II/V_5$ while more recent data support the use of $II/V_3$ or $V_4$. Full 12-lead ECG analysis should occur on arrival to the ICU. At Hopkins, we have also decided to repeat the ECG at 4 and 8 h, as well as daily on POD 1 and 2.

A chest x-ray is mandatory in all patients to verify (1) the positioning of the endotracheal tube, which is generally halfway between the carina and the sternal notch, (2) that there is no undrained effusion, usually the result of inadequate evacuation in the operating room, (3) that there is no pneumothorax, (4) that there are no unexpected infiltrates, and (5) that the invasive tubes and central venous or pulmonary catheters are well positioned. Left lower lobe atelectasis with silhouetting of the left hemidiaphragm is the rule, although this may not be evident until positive pressure ventilation is discontinued. It should not be overinterpreted.

Routine postoperative laboratory tests should include hemoglobin or hematocrit, sodium and potassium, glucose, calcium, and arterial blood gas; these should be obtained every 4 to 8 h or more frequently when clinically indicated. Additional hematologic and chemistry tests need not be routine but should be obtained based on clinical signs/symptoms.

A central venous catheter is mandatory for the administration of vasoactive drugs. However, the need for a central venous catheter versus a pulmonary artery (PA) catheter

**TABLE 26-1: Anatomic, Physiologic, and Clinical Consequences of Cardiac Surgery and Cardiopulmonary Bypass**

| Stressor | Pathophysiologic Sequelae | Clinical Sequelae |
|---|---|---|
| Anatomic | | |
| Aortic cannulation/decannulation | Aortic atheroembolism | Stroke (large vessel) |
| Aortic cross-clamping/unclamping | Myocardial ischemia/reperfusion injury | LV and RV dysfunction/low CO |
| | Aortic atheroembolism | Atrial and ventricular arrhythmias |
| | | Stroke (large vessel) |
| Cardiac manipulation/positioning | Aortic atheroembolism | Stroke (large vessel) |
| | Decreased cardiac output (OPCAB) | Prerenal azotemia, hepatic, mesenteric insufficiency |
| Atrial cannulation | Atrial trauma | Atrial arrhythmias |
| Pericardiotomy | Pericardial inflammation | Atrial arrhythmias |
| Valve replacement | Septal trauma | AV conduction block |
| | Cordal attachment to valve severed (mitral only) | LV dysfunction/low CO |
| Physiologic | | |
| Extracorporeal circulation | Activation of contact activation pathway of coagulation | Need for heparin/protamine coagulopathy |
| | Activation of fibrinolytic systems | Coagulopathy |
| | Activation of systemic inflammation (complement, leukocytes, cytokines) | SIRS |
| | | Capillary leak syndrome |
| | | Inflammatory end organ damage to brain, heart, lung, and kidney |
| | Microembolization | Stroke (small vessel) |
| Controlled hypotension (MAP = 40–60 mm Hg) | Systemic hypoperfusion | Stroke (watershed) |
| | Sympathetic activation | Arrhythmias |
| | Renin–angiotensin release | BP lability |
| | | Prerenal azotemia, hepatic, mesenteric insufficiency |
| Nonpulsatile blood flow | Systemic hypoperfusion | Stroke (watershed) |
| | Sympathetic activation | Arrhythmias |
| | Renin–angiotensin release | BP lability |
| | | Prerenal azotemia, hepatic, mesenteric insufficiency |
| Hypothermia | Decreased efficiency of coagulation cascade | Coagulopathy |
| | Shivering/increased $O_2$ consumption and $CO_2$ production | Hypercarbia/ventilatory insufficiency |
| | Sympathetic activation | Arrhythmias |
| | | BP lability |

LV, left ventricular; RV, right ventricular; CO, cardiac output; OPCAB, off-pump coronary a rtery bypass; AV, atrioventricular; SIRS, systemic inflammatory response syndrome; MAP, mean arterial pressure; BP, blood pressure.

remains controversial. Although the PA catheter can provide hemodynamic information about a patient's status that might otherwise be difficult to determine, it has yet to be incontrovertibly demonstrated that this information improves patient outcome.

For example, one prospective randomized trial in critically ill patients failed to demonstrate the benefit of PA catheter–directed management compared with a central venous catheter alone[1]; however, a prospective, randomized study in postoperative cardiac surgery patients in which goal-directed therapy was protocolized did show benefit.[2] In the face of this evidence, PA catheters probably need not be routinely used, but when hemodynamics are tenuous and incompletely understood, the information gained from better understanding the patient's cardiac output, filling pressures, pulmonary arterial pressures, and oxygen delivery can significantly impact on therapeutic decision making.

## Hypothermia

During cardiac surgery when cardiac arrest is anticipated, hypothermia is deliberately induced intraoperatively to protect organs from ischemic injury during periods of diminished blood flow. The ability of hypothermia to reduce ischemic organ damage, particularly in the brain, has been shown in a number of animal models and clinical settings. In a prospective randomized trial of hypothermic (28°C–32°C) versus normothermic (37°C) CPB for coronary revascularization, normothermia was associated with a worse neurologic outcome.[3] The degree to which hypothermia should be induced has changed; however, temperatures less than 30°C are associated with higher mortality, increased cardiac dysfunction, more renal injury, coagulation factor and platelet dysfunction, an increased inflammatory response, and an increased incidence of wound infections (see Table 26-1). It

now appears that although a few degrees of hypothermia are beneficial for brain preservation, more severe hypothermia than that appears to be deleterious.[4]

To mitigate the adverse effects of hypothermia in the postoperative period, active warming should be initiated postoperatively with a goal of restoring temperature between 36°C and 37°C. Although a number of warming methods are available, forced-air warming devices appear to be the most effective.

## Cardiovascular System

### HEMODYNAMICS

Hemodynamic instability is common in the early postoperative phase of cardiac surgery. Intraoperative insults (see Table 26-1) frequently have an adverse impact on cardiovascular function. For example, preoperative ischemia, ischemia-reperfusion injury, and CPB-related inflammation all contribute to depressed myocardial contractility after cardiac surgery. In most patients, this dysfunction resolves within 24 h; however, inotropic support may be required until this transient dysfunction resolves. Patients with ventricular dysfunction prior to surgery are more likely to require more inotropic support than those with normal ventricular function.

Inadequate preload, the result of relative intravascular hypovolemia, occurs routinely and can be a major contributor to poor cardiac output and unstable hemodynamics. The causes of intravascular volume depletion are threefold: bleeding, which occurs to a variable degree but averages approximately 400 to 500 $cm^3$ per case; warming and the temperature-dependent opening of vascular beds, most notable when patients return to the ICU cold (that is, less than 36°C); and third space losses, the sequelae of CPB-induced abnormalities that result in systemic inflammation. These three determinants of intravascular volume play an active role for the first 6 to 10 h postoperatively. Thereafter, volume resuscitation to maintain adequate preload should not be required. Should significant volume requirements persist to maintain adequate preload in the face of low cardiac output, other adverse clinical causes should be sought, for example, tension pneumothorax, tamponade, valvular dysfunction, or cardiac ischemia. Finally, despite adequate preload and cardiac function, vascular tone can be excessively high from adrenergic hyperactivation or low from CPB-induced systemic inflammatory response syndrome (SIRS). Thus, transient infusions of vasodilators or vasoconstrictors, separate and apart from inotropic agents, may be needed until vascular stability returns, again, almost always within 24 h of surgery.

The goal of hemodynamic management in the early postoperative phase is to maintain adequate oxygen delivery to the tissues by optimizing cardiac performance. In all cases, this relies on the caregiver to optimize preload and afterload, and thereafter, use inotropic agents or mechanical assist devices, most commonly the intra-aortic balloon pump and rarely a ventricular assist device.

Cardiac performance is reflected in the cardiac index, which normally ranges from 2.4 to 4.2 L/min/$m^2$. However, "normal" cardiac performance in patients after cardiac surgery is not clearly defined, and attempting to reach a specific "value," for example, a cardiac index (CI) of 2.4 L/min/$m^2$ can be self-defeating. Ventricular dysfunction is ubiquitous in the early postoperative period; adequacy of perfusion, therefore, must be determined clinically, though frequently guided by a more quantitative assessment of myocardial performance. Clinical targets that reflect adequate cardiac output are (1) a mean arterial pressure (MAP) adequate for renal, splanchnic, and cerebral perfusion, usually 60 to 85 mm Hg; (2) warm extremities with palpable pedal pulses; (3) urine output of 0.5 mL/kg/h; and (4) the ability to mentate. As mentioned earlier, invasive monitors, such as a PA catheter, can be extremely useful to guide therapeutic decision making, but frequently ideal hemodynamics are not possible to obtain. A CI of 2.0 to 2.2 L/min/$m^2$ is generally adequate immediately following cardiac surgery. Monitoring of mixed venous oxygen saturation, from either intermittent blood sampling or continuous invasive cooximetry, can provide data to complement other information. As a general guideline, a mixed venous saturation of 60 to 70 percent, with an arteriovenous oxygen difference of less than 5 to 6 $cm^3$/dL is adequate. Mixed venous oxygen saturations of less than 50 percent and larger A-$Vo_2$ differences are markers of inadequate oxygen delivery. Invariably, poor oxygen delivery results in an increase in the base deficit with the development of a lactic acidosis, so a blood gas and serum lactate level can be used to help track the adequacy of hemodynamic resuscitation.

Patients who do not exhibit adequate perfusion need immediate resuscitation before end-organ compromise occurs. Frequently, direct cardiac output and intracardiac pressure monitoring using a PA catheter can be particularly useful to diagnose the patient's condition and guide therapy. Furthermore, despite an initial ECG and chest x-ray that may have been acceptable, when inadequate perfusion is recalcitrant to what is perceived as adequate intervention, a repeat ECG and chest x-ray are always in order. Furthermore, a cardiac echocardiogram can be very useful, particularly when tamponade and ventricular dysfunction are part of the differential diagnosis.

When adequate perfusion is an issue, a large number of inotropic and vasoactive agents are available to support the circulation. Each of these agents has particular pharmacokinetic and pharmacodynamic properties that may be more or less advantageous in any single patient (Table 26-2). Although there is no evidence indicating a difference in patient outcome based on selection of vasoactive drug, an astute clinician should be familiar with the theoretic advantages of each agent so as to be able to select agents appropriate to the particular circumstance at hand. Regardless, if oxygen delivery is still marginal after optimization of preload and afterload and the addition of significant inotropic agents, strong consideration should be given to placement of an intra-aortic balloon pump. An intra-aortic balloon pump can be expected to increase coronary perfusion due to diastolic augmentation

**TABLE 26-2: Vasoactive Agents, Dosing, Hemodynamic and Adverse Effects**

| | Vasoconstrict | Vasodilate | Contractility | HR | BP | CO | $t_{1/2}$ | Adverse Effects |
|---|---|---|---|---|---|---|---|---|
| VAP | +++ | – | – | 0/↓ | ↑ | ↓ | 10–20 min | Organ ischemia |
| 0.01–0.04 (U/min) | VAP-R | | | | | | | |
| PNE | ++/+++ | – | – | 0/↓ | ↑ | ↓ | 150 min | Organ ischemia |
| 0.1–2.0 (μg/kg/min) | $\alpha_1$-R | | | | | | | |
| NE | ++++ | 0/+ | +++/++++ | 0/↓ | ↑↑ | 0/↓ | 1.45–2.90 min | Organ ischemia |
| 0.01–0.5 (μg/kg/min) | $\alpha_1$-R | $\beta_2$-R | $\beta_1$-R | | | | | Arrhythmias |
| EPI | ++++ | ++++ | ++++ | ↑ | ↑↑ | ↓/0/↑ | Approx 2 min | Organ ischemia |
| 0.01–0.5 (μg/kg/min) | $\alpha_1$-R | $\beta_2$-R | $\beta_1$-R | | | | | Arrhythmias |
| DA | +++ | + | +++ | ↑ | ↑ | ↓/0/↑ | 2 min | Organ ischemia |
| 1.0–20 (μg/kg/min) | $\alpha_1$-R | $\beta_2$-R<br>+++<br>$DA_1$-R | $\beta_1$-R | | | | | Arrhythmias |
| DOB | – | +++ | +++ | 0/↑ | 0/↓ | ↑ | 2 min | Hypotension |
| 1.0–20 (μg/kg/min) | | $\beta_2$-R | $\beta_1$-R | | | | | Arrhythmias |
| ISOP | – | ++++ | ++++ | ↑↑ | ↓↓ | ↑↑ | 2.5–5 min | Hypotension |
| 0.01–0.5 (μg/kg/min) | | $\beta_2$-R | $\beta_1$-R | | | | | Arrhythmias<br>Myocardial ischemia |
| MIL | – | +++ | +++ | 0/↑ | ↓ | ↑ | 2–3 h | Hypotension |
| 0.3–0.8* (μg/kg/min) | | PDEI | PDEI | | | | | |
| NES | – | ++ | – | 0 | ↓ | ↑ | 18–23 min | Hypotension |
| 0.01–0.03[a] (μg/kg/min) | | ANP | | | | | | |
| FEN | – | +++ | – | 0 | ↓ | ↑ | 9.8 min | Hypotension |
| 0.03–0.16 (μg/kg/min) | | $DA_1$-R | | | | | | |

ANP, atrial natriuretic peptide; BP, blood pressure; CO, cardiac output; DA, dopamine; DOB, dobutamine; EPI, epinephrine; FEN, fenoldopam; HR, heart rate; ISOP, isoproterenol; MIL, milrinone; NE, norepinephrine; NES, nesiritide; PDEI, phosphodiesterase inhibition; PNE, phenylephrine; R, receptor; $t_{1/2}$, plasma half-life; VAP, vasopressin; ↑, increase; 0, no effect; ↓, decrease.
[a]Loading dose required.

of pressure and to further diminish afterload as a result of active balloon emptying timed to systole. Although increased perfusion may be less than 500 $cm^3$/min as a result of the balloon mechanics itself, clinically the change in the balance of myocardial oxygen supply and demand can be considerable, leading to vastly improved cardiac performance, with improvement in the CI by as much as 50 percent and mixed venous oxygen saturation by as much as 15 to 20 percent.[5,6]

Furthermore, to the degree that the catecholamine requirements are diminished as a result of the balloon pump, adrenergic causes of cardiac arrhythmias can be mitigated and at times, intractable arrhythmias can resolve.

***Myocardial Ischemia.*** The presence of ECG and echocardiographic evidence of myocardial ischemia appears frequently in the first several hours after coronary revascularization and, if indicative of ongoing cardiac ischemia, is predictably associated with an adverse outcome.[7] However, in the majority of patients who undergo cardiac surgery, early ECG changes are nonspecific and do not represent clinically or hemodynamically meaningful ischemia. However, poor cardiac indices, evidence of shock, high central filling pressures, and arrhythmias all suggest ongoing ischemia and poor ventricular function. In this setting, the presence of regional abnormalities on ECG or segmental wall motion abnormalities by echo support the diagnosis of significant myocardial ischemia. Beta-blockade and antiplatelet/anticoagulant therapy, the therapeutic mainstays for myocardial ischemia in other settings, are generally not useful immediately after cardiac surgery because of the invariable need for inotropes, not myocardial depressants, and the risk of exacerbating postoperative bleeding. Intravenous infusion of nitroglycerin or a calcium channel antagonist may be useful, particularly in cases of internal mammary artery (IMA) spasm[8]; however, hypotension often precludes their use as well.

Medical management of myocardial ischemia after cardiac surgery is limited to physiologic manipulations aimed at preventing shock by optimizing myocardial $O_2$ supply and demand. Improving cardiac output, as always, requires optimization of preload and afterload, and then the addition of inotropic agents. Although evidence supports transfusion of red blood cells to a hemoglobin of 10 to 11 g/dL in patients above 65 years of age with ongoing myocardial ischemia, the applicability of this to the postoperative cardiac surgery patients is questionable, as blood transfusions appear to be associated with a poorer outcome in this patient group.[9] Nevertheless, it is hard to argue against the correction of anemia in the face of ongoing myocardial ischemia. Whether or not medical management is successful in the treatment of postoperative shock

due to ongoing ischemia, consideration of invasive therapy is always warranted, including insertion of an intra-aortic balloon pump, percutaneous coronary intervention, or surgical reexploration and repeat coronary bypass grafting.[5]

***Arrhythmias.*** Supraventricular and ventricular arrhythmias occur commonly after cardiac surgery. A number of factors associated with an increased risk of postoperative arrhythmias have been identified: advanced age, preoperative history of arrhythmia, history of congestive heart failure, use of bicaval venous cannulation, and longer duration of CPB. In addition to arrhythmogenic intraoperative events (see Table 26-1), a number of postoperative conditions can incite arrhythmias as well, for example, sympathetic hyperactivity, myocardial ischemia, electrolyte disturbances, atrial distention, mechanical irritation from an indwelling central venous line, and drug therapies. As in all clinical settings, hemodynamically unstable arrhythmias require immediate attention and treatment, often including cardioversion/defibrillation.

**Bradycardia:** Sinus bradycardia, junctional rhythm, and atrioventricular (AV) conduction disturbances comprise the majority of bradycardic rhythms after cardiac surgery. Perioperative drug therapies (β-blockers, digoxin, or amiodarone), hypothermia, electrolyte disturbances, and direct trauma to conductive tissue may all contribute to the development of bradycardia. High-grade conduction blockade (i.e., new bifascicular or trifascicular block and complete heart block) is the most serious of these as it is frequently associated with significant hemodynamic compromise and reflects an intraoperative injury to the conduction system that may be permanent. Infusion of $\beta_1$-agonists (see Table 26-2) frequently can increase heart rate and perfusion, but pacing is the simplest method of treating any postoperative, symptomatic bradycardia. In this circumstance, whenever possible, AV synchrony should be preserved by simple atrial pacing as stroke volume is greater when the electrical impulse is generated at or above the AV node, with the resultant coincident synchrony of ventricular systole.[10] In patients who require pacing, the rule of thumb is that atrial pacing is favored over AV sequential pacing, which is favored over ventricular pacing. Most patients who have significant AV conduction block that persists 5 to 7 days after surgery require permanent pacemaker placement.

**Supraventricular arrhythmia:** Without prophylaxis, supraventricular tachycardia occurs in 30 to 40 percent of patients undergoing cardiac surgery, more frequent after valve surgery than coronary artery bypass grafting (CABG). The vast majority of supraventricular tachycardia after cardiac surgery is atrial fibrillation (AF) or flutter, which most commonly develops between postoperative days 1 and 4, with peak incidence on days 2 and 3. These two rhythm disturbances are associated with an increased length of hospital stay, higher cost, and increased risk of stroke. In poorly contractile ventricles, it can lead to hemodynamic compromise. The incidence of AF can be reduced by approximately 50 percent by the initiation of prophylactic treatment with β-blockers, amiodarone, or sotalol.[11] Preoperative loading with amiodarone is more effective than postoperative loading; however, both methods reduce the incidence of AF. Daily magnesium started preoperatively and continued for 4 days postoperatively has also been shown to reduce the incidence of AF after CABG. When AF does develop, initial therapy should be directed at assuring hemodynamic stability and rate control. Cardioversion should be used in patients who are hemodynamically unstable. A rapid ventricular response can usually be controlled with intravenous β- or calcium channel blockers, although β-blockers may be superior in the perioperative period. Intravenous amiodarone may be preferable for rate control in patients with reduced LV function (ejection fraction below 40 percent) because it is less negatively inotropic than β- or calcium channel blockers. At Johns Hopkins, currently amiodarone is the drug of choice for postoperative AF, both for rate control and conversion to sinus rhythm.

**Ventricular arrhythmias:** Unexpected, prolonged postoperative ventricular ectopy is unusual and ischemia as a cause should be ruled out. In the face of ischemia, antiarrhythmic therapy may be indicated. It goes without saying that patients who develop sustained ventricular tachycardia or ventricular fibrillation should be cardioverted and/or defibrillated and treated with an antiarrhythmic agent. Amiodarone is the pharmacologic agent of choice according to present American Heart Association (AHA) guidelines. Patients who do experience significant ectopy and/or sudden cardiac death (i.e., in-hospital cardiac arrest) without a reversible cause should be considered for an electrophysiologic study. Particularly in the setting of poor ventricular function, implantation of an automatic internal cardioverter defibrillator (AICD) may improve survival.[12]

## Antiplatelet Therapy and Saphenous Vein Graft Patency

Over the past 20 years, advances in harvesting techniques and the recognition of their impact on outcome have increased the use of arterial grafts for coronary artery bypass surgery, as opposed to the sole use of saphenous vein grafts. Indeed, the IMA has become the standard conduit for the left anterior descending (LAD) artery bypass due to its enhanced (90 percent) patency at 10 years, virtually free of disease. This contrasts dramatically to vein grafts, which show only a 60-percent patency at 10 years, with half of the patent grafts containing significant stenosis.[13] Arterial grafts appear protected from the atherosclerosis that occurs with arterialized vein grafts that clearly is one explanation for their superior patency. However, native coronary artery competitive blood flow contributes to early loss of arterial grafts, implying that below a certain threshold of proximal coronary artery stenosis, arterial conduits should not be used. This is particularly true of the radial artery. In situations where atherosclerosis is clear, but stenosis may not be critically tight, vein grafts

appear superior to arterial ones. The above notwithstanding, an improved survival appears to be most affected by utilization of the left IMA to bypass the LAD coronary. Percent utilization of this conduit for the LAD bypass is a requirement for public reporting by all open heart surgery programs as it reflects the quality of the surgery performed. The top 10 percent of cardiac programs use this conduit for the LAD in over 90 percent of coronary bypass procedures.

A great deal of work has been done in attempting to elucidate the mechanisms underlying vein graft occlusion, in an effort to predict risk factors for graft failure, and to develop therapies to prolong vein graft patency. Postoperative occlusion of vein grafts is a major risk factor for the recurrence of symptoms leading to reoperations for coronary occlusive disease. Hyperlipidemia, low ejection fraction, male gender, cigarette smoking, and a history of prior myocardial infarction are clinical predictors of poor long-term graft patency.

However, short-term graft patency (<1 month after surgery) is determined by intraoperative factors, technical errors in distal or proximal anastomoses, the size and quality of the recipient artery, injury to the vein during its harvest, and low flow rates through the conduit after completion of the anastomosis (≤40 mL/min). Approximately 5 to 10 percent of vein grafts are lost by postoperative day 7, most of these grafts occluding silently. In the early postoperative period, when graft loss is suspected and the patient is hemodynamically compromised, reoperation or catheterization with an eye toward percutaneous revascularization may be indicated.

The mainstay of medical therapy to improve early graft patency relies on antiplatelet drugs, most commonly aspirin (ASA), which has been shown to make a significant difference in 1-week- and 1-year vein graft patency. Aspirin irreversibly blocks platelet aggregation by inhibiting cyclooxygenase-1 (COX-1) and preventing thromboxane A2 production. It lasts the lifetime of the platelet (~7–10 days). In the VA Cooperative Study in the late 1980s, its effects were most profound on the bypasses to smaller vessels. The greatest efficacy at maintaining SVG patency with the least risk of bleeding was demonstrated when ASA was given within the first 6 h postoperatively, but not preoperatively. Although ASA therapy does not appear to have any beneficial effects on vein graft patency after the first year (SVG patency is 95 percent at 1 week, 84 percent at 1 year, 80 percent at 3 years, 69 percent at 6 years, and 61 percent at 10 years), most surgeons and cardiologists continue aspirin indefinitely due to its beneficial effects on the myocardium and general vascular health.[14]

Clopidogrel, a thienopyridine antiplatelet agent, inhibits ADP-dependent platelet activation and aggregation, thus acting on platelets in a manner different from ASA. Most of the initial work with clopidogrel was done in patients with acute coronary syndromes (ACSs), the results of which have led to its virtually universal preprocedural administration in patients undergoing percutaneous interventions (PCIs). Although the risk of bleeding with preoperative ASA has been found to be present but manageable, the risk of major bleeding after clopidogrel is much higher, and prompts many surgeons to delay surgery if possible. Postoperatively, daily clopidogrel use has been associated with a 33-percent reduction in the incidence of recurrent ischemic events over a 4- to 5-year period. However, the increased risk of gastrointestinal (GI) complications associated with prolonged clopidogrel use as well as its association with increased bleeding and surgical site infections mitigates against its routine postoperative use. Oral anticoagulation has shown no benefit compared with ASA in improving graft patency or diminishing major adverse cardiac events (MACE), but clearly it increases bleeding complications. Another class of antiplatelet therapy, glycoprotein IIb/IIIa inhibitors, though beneficial in the settings of ACSs, has not been studied in postoperative CABG patients.

In summary, the most recent recommendations from the American Heart Association/American College of Chest Physicians (AHA/ACCP) include the following: (1) All patients undergoing CABG receive 75 to 162 mg ASA per day, starting within 6 h of operation, or as soon as possible if postoperative bleeding events preclude earlier administration; (2) For those patients allergic to ASA, clopidogrel given as a loading dose of 300 mg within 6 h after surgery followed by 75 mg daily is considered equivalent; (3) Patients undergoing CABG for non-ST elevation ACS receive clopidogrel 75 mg daily for 9 to 12 months after surgery in addition to aspirin; (4) Patients already on clopidogrel for an ACS should stop the drug 5 days prior to scheduled CABG; (5) All patients who undergo CABG with IMA grafts receive 75 to 162 mg aspirin daily, indefinitely.[15]

## Statin Therapy

Statin (3-hydroxy-3-methylglutaryl-coenzyme- alpha- reductase inhibitor) therapy has been shown to reduce the risk of adverse coronary events and all-cause mortality in patients with stable CAD, ACS, and in post-cardiac surgery patients. Early therapy after acute coronary events has been shown to improve outcomes in patients with unstable disease. Statin-mediated effects in stable and unstable CAD are hypothesized to be due to the anti-inflammatory and immunomodulatory "pleiotropic" characteristics of the drugs, in addition to their cholesterol-lowering effects. Convincingly, a recent meta-analysis demonstrated that preoperative statin therapy resulted in a 43-percent odds reduction of early all-cause mortality as well as a significant reduction in AF and stroke.[16]

The risks of initiating or continuing preoperative statin therapy in postoperative cardiac patients, particularly as regards rhabdomyolysis, myopathy, hepatotoxicity, and acute renal failure are small, outweighed by the overwhelming evidence of their protective effects on the myocardium and endothelium. The controversy over the optimum dosage, however, has not yet been resolved. Further trials are needed to determine whether benefits of statins when administered in high dosages outweigh their risks. In addition, caution is advised when prescribing these drugs for patients on immunosuppression (e.g., liver or cardiac transplant recipients), or those with evidence of liver failure.

At Johns Hopkins, we have adopted a policy of placing all patients on postoperative statins as soon as they are able

to tolerate oral medications. Most patients who undergo cardiac surgery have been prescribed statins already. We use an elevation of hepatic enzymes of 3 to 4 times normal as a contraindication to starting or continuing statin therapy, although there are no data expressly supporting this cut-off.

## PULMONARY SYSTEM

Cardiac surgery is associated with a marked reduction in pulmonary function that peaks 24 h after surgery and gradually improves over the next several weeks. The pulmonary defect is characterized by a 30 to 50 percent reduction in forced vital capacity (FVC) and forced expiratory volume ($FEV_1$), reflecting a restrictive lung defect in all patients. There is an increase in lung edema, an increase in atelectasis (almost universally, the left lower lobe is collapsed postoperatively), a decrease in pulmonary compliance, widening of the alveolar–arterial $O_2$ gradient, and increase in the work of breathing. The clinical significance of these gas exchange and restrictive lung defects is dependent on the degree of pulmonary compromise present prior to surgery. For patients with normal pulmonary function, the reduction in pulmonary mechanics and gas exchange has limited clinical consequences; but for those with significant preexisting pulmonary deficits, the new abnormalities can lead to respiratory failure. Parenchymal lung injury from CPB-related SIRS and ischemia/reperfusion injury contributes substantially to postoperative lung dysfunction, and the development of respiratory failure is related to the duration of CPB (see Table 26-1). Although a reduction in pulmonary mechanics is ubiquitous, clinically it is uncommon for patients to suffer respiratory failure (defined as the need for mechanical ventilation for more than 72 h). Diaphragmatic dysfunction from phrenic nerve injury may occur in some patients. However, in this setting, significant respiratory insufficiency does not usually occur unless the injury is bilateral.

Because the CBP-injured lung is susceptible to edema formation, even at relatively low filling pressures, fluid management is a key component of strategies designed to reduce pulmonary complications. As a result, management of the postoperative hemodynamics involves a balance between the benefits of preload augmentation and the risks of pulmonary edema formation. As a general rule, postoperative fluids should be administered in a way that assures adequate hemodynamics at the lowest possible filling pressures; when postoperative SIRS abates, diuresis should begin, usually on postoperative day 1.

### Ventilator Management

The vast majority of patients who undergo cardiac surgery are transferred from the operating room to the ICU with an endotracheal tube in place. In the early postoperative period (the first 24 h), the need for mechanical ventilatory support is based on the following principles: (1) airway protection; (2) oxygenation and ventilation; and (3) the provision of a margin of safety for patients who may encounter significant challenges from hemodynamic instability, acute hemorrhage, and acid/base abnormalities. Weaning from mechanical ventilation in this early period is a matter of providing appropriate support for the pulmonary system until the acute, hemodynamic issues resolve, and then determining the adequacy of oxygenation and ventilation with minimal support, for example, 40 percent oxygen, PEEP of 5 $cmH_2O$, and pressure support of 5 $cmH_2O$. At that point, extubation can be undertaken. (Criteria for initiating the weaning/extubation process are listed in Table 26-3.)

Prolonged mechanical ventilation, although often life-sustaining, is associated with significant complications including barotrauma, oxygen toxicity, glottic and tracheal injury, decreased cardiac output, and pneumonia. Extubation should be sought at the earliest possible time in all patients, taking into consideration that patients who are extubated prematurely and require reintubation have an increased risk of nosocomial pneumonia and an increased mortality risk as well. The challenge for the clinician is to recognize those patients ready for weaning and to time their extubation appropriately. At Hopkins, the median time to extubation for all patients is less than 9 h; but intubation for longer than 24 h occurs in 20 percent of patients.

**TABLE 26-3: Ventilator Weaning and Extubation Criteria**

| | |
|---|---|
| **General criteria** | Clinical status improving |
| | Hemodynamically stable[a] (MAP >65, CI >2 L/min/m²) |
| | Chest tube drainage <50 mL/h |
| | 36°C > temp < 38°C |
| | No shivering |
| **Airway protection criteria** | Awake, follows commands |
| | Cough and gag intact |
| | Muscle strength adequate (patient capable of 5-s head lift) |
| | Pulmonary secretions manageable |
| **Gas exchange criteria** | pH >7.32 |
| | $P_{CO_2}$ <52 mm Hg |
| | $P_{a_{O_2}}$ >70 mm Hg on 40% $O_2$, PEEP 5 $cmH_2O$ |
| **Ventilatory reserve criteria** | f/TV <80 during spontaneous breathing trial on pressure support of 5 $cmH_2O$ or T-piece |
| | Respiratory rate <30 |
| | Negative inspiratory force >−25 $cmH_2O$ |
| | Forced vital capacity >10 mL/kg |

MAP, mean arterial pressure; CI, cardiac index; f/TV, frequency of breathing (i.e., respiratory rate)/tidal volume (expressed as liters).

[a]Pressors/inotropes and circulatory assist devices (e.g., intra-aortic balloon pump) are permitted if doses are not escalating and active titration is not required.

In those patients who have sustained a significant perioperative lung injury, ventilator strategies that reduce tidal volumes (≤6mL/kg) and inspiratory pressures (plateau pressure below 30 $cmH_2O$) have been shown to shorten recovery time and improve survival.[17] The fraction of inspired oxygen ($FIO_2$) should be reduced to 0.5 as quickly as tolerated to reduce potential for oxygen toxicity. Increasing PEEP improves V/Q matching in most patients and facilitates reduction in $FIO_2$.

Ventilator-associated pneumonia (VAP) (defined as a pneumonia that develops 48 h or more after initiation of mechanical ventilation) accounts for a significant, often preventable, complication in critically ill patients. The most recent data suggest that while rates (expressed as cases/1000 ventilator days) have decreased over the past decade, the incidence of VAP is still unacceptably high: 8.1 in trauma, 4.9 in surgical ICUs, and 3.9 in cardiac ICUs.[18] Ventilated patients who develop VAP have a higher mortality than those who do not (46 vs 32 percent, respectively), while those with VAP also spend longer on the ventilator, in the ICU, and in the hospital. As a point of reference, cardiac surgery patients have an incidence of postoperative pneumonia of approximately 1 percent, and as mentioned above, a VAP rate of approximately 4 cases per 1000 ventilator-days.

In 2002, VAP bundles (a "bundle" is a group of interventions related to a disease process that, when executed together, results in better outcomes) were first described as interventions to reduce the incidence and adverse sequelae of VAP. Over the past several years, institutions have refined the bundle initially outlined by the Institute for Healthcare Improvement (IHI) such that it now includes the following five elements: head-of-bed (HOB) elevation, daily sedation "holidays" and assessment of readiness to extubate, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis, and daily oral care with chlorhexidine.[19] Implementing all these interventions, however, requires buy-in by the relevant multidisciplinary stakeholders, daily goal setting during physician and nursing rounds, and regular process evaluation and feedback. At Johns Hopkins, it is our routine practice to follow the VAP bundle as currently recommended, a care measure that is an integral part of our daily patient care checklist.

In patients experiencing prolonged intubation, traditional strategies for ventilator weaning include a gradual reduction in the rate of intermittent mandatory ventilation (IMV) or in the level of pressure-support ventilation. Some studies suggest a benefit of pressure-support weaning over IMV weaning, others with a simple, once a day trial of spontaneous breathing. The ability to successfully wean patients from mechanical ventilation may be improved by combining daily spontaneous weaning trials with useful elements from other weaning modalities along with highly predictive extubation criteria [e.g., respiratory rate/tidal volume (L) <80 (also called the rapid shallow breathing index)]. At the moment, in patients who have had median sternotomies and have failed to wean from the ventilator, we perform a tracheostomy no sooner than day 10. Although the evidence is scant, we wait until then for fear of an increased risk of a deep sternal wound infection due to the tracheostomy.

## RENAL SYSTEM

Half of all patients who undergo cardiac surgery will experience a significant reduction in renal function (defined as an increase in serum creatinine greater than 25 percent of baseline). Along with the rise in creatinine seen so often, more significant deterioration in renal function requiring dialysis also presents itself all too frequently, occurring in 4 to 5 percent of patients. Analogous to postoperative pulmonary dysfunction, the development of clinically significant renal dysfunction is directly linked to the severity of preoperative renal impairment.[20] Additional preoperative risk factors for the development of renal insufficiency include valve surgery (vs CABG), reduced LV function, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), and the use of an intra-aortic balloon pump. Despite improvements in renal replacement therapy over the past 25 years, mortality for patients who develop acute renal failure remains approximately 50 percent, with mortality now largely attributable to respiratory, infectious, and bleeding complications instead of renal failure per se.

The overwhelming majority of cases of acute renal insufficiency that develop after cardiac surgery are due to acute tubular necrosis (ATN). The pathophysiologic basis for ATN in cardiac surgery stems from a combination of prerenal causes that progress to frank renal ischemia. Systemic inflammation, renal atheroembolization, and nephrotoxins also contribute to the development of renal dysfunction in this setting. As can be seen in Table 26-1, a variety of intraoperative events (e.g., CPB, controlled hypotension, nonpulsatile blood flow, aortic cross clamping, etc.) can promote the development of renal insufficiency. Postoperatively, renal dysfunction can be exacerbated by persistent hemodynamic instability (i.e., low cardiac output, hypotension, and elevated venous pressures, which overall decrease perfusion pressure).

Management of perioperative renal insufficiency can be divided into two overlapping processes: strategies to prevent the development of renal insufficiency and strategies to treat established renal dysfunction. The mainstay of therapy in both processes is to maintain adequate hemodynamics, targeting a CI and BP to provide adequate renal perfusion. Generally, a CI greater than 2.2 $L/min/m^2$ and MAP greater than 65 to 70 mm Hg is adequate. Recognition that normotensive renal insufficiency can play a role is important, since in some patients, renal perfusion and glomerular filtration will be very afferent pressure-sensitive. In this patient population, invariably those with longstanding, uncontrolled hypertension, afterload reduction to facilitate ventricular stroke volume may lead to a significant prerenal state. Tolerance of higher systemic BPs may be required to maintain renal perfusion. The mortality associated with renal failure is so significant that in the face of a rising creatinine, assurance of adequate perfusion is paramount. When unclear, the threshold for invasive monitoring, for example, PA catheterization and cardiac output assessment and echocardiography should be lowered. In addition to hemodynamic management, nephrotoxins should be discontinued whenever possible.

Nonsteroidal anti-inflammatory agents and angiotensin converting enzyme inhibitors are two commonly used drugs that should be avoided in the setting of acute renal dysfunction.

A number of agents including diuretics (furosemide, mannitol), dopamine, and, more recently, fenoldopam (a selective dopamine$_1$ receptor agonist) are purported to be renoprotective. Nevertheless, data do not support their use for prophylaxis against renal failure in cardiac surgery. Unfortunately, once renal dysfunction has occurred there are no specific therapies for its amelioration; treatment is supportive only. The atrial natriuretic peptide, anaratide, initially showed promise for the treatment of ATN, but subsequent investigations have shown no benefit. Another natriuretic peptide, nesiritide, has proven to be of benefit in the treatment of decompensated heart failure and may have benefit in the treatment of postoperative patients with congestive heart failure and concurrent renal dysfunction. Nevertheless, to this point, its benefit is not clear, and its expense and the risk associated with its use (severe hypotension) may outweigh any benefit derived.

The mainstay of treatment for renal dysfunction begins by ensuring adequate hemodynamics and avoiding nephrotoxins. Once prerenal and postrenal causes have been ruled out, management of established renal insufficiency is focused on attempting to maintain appropriate fluid and electrolyte balance. Fluid intake should be kept to a minimum. In oliguric patients, diuretics can be administered in an attempt to improve urine output and facilitate fluid management and the treatment of hyperkalemia. Although nonoliguric renal failure has a better prognosis than oliguric renal failure, data are limited that the use of diuretics to induce a nonoliguric state changes the overall outcome. Nonetheless, fluid and electrolyte management is simplified in patients in whom diuretics improve urine output.

## Dialysis

The indications for dialysis in renal failure following cardiac surgery are the same as in other settings: fluid overload, hyperkalemia, acidosis, and uremia. Renal replacement therapy can be provided as conventional intermittent hemodialysis (IHD) or as continuous hemodialysis (usually as veno–veno hemodialysis, or CVVHD). A comparison of the two modes is shown in Table 26-4. The major advantage of IHD—rapidity of clearance and fluid removal—is also its major disadvantage; it can lead to hemodynamic instability, not encountered to any significant degree with CVVHD. When IHD is chosen for stable patients, recent data demonstrate that daily hemodialysis improves renal recovery and survival better than every-other-day dialysis.

# GASTROINTESTINAL SYSTEM

GI complications occur in approximately 1 percent of patients undergoing cardiac surgery. The most common complication is upper GI bleeding, usually from duodenal or gastric ulceration. Ileus, pancreatitis, and mesenteric ischemia may also occur. Splanchnic hypoperfusion during CPB is purported to be the pathophysiologic mechanism underlying these complications, although embolization to the splanchnic bed during intraoperative aortic manipulation may also play a role. In those patients who develop acute mesenteric ischemia, mortality is high.

Patients undergoing cardiac surgery should receive stress ulcer prophylaxis. Although the appropriate duration of prophylaxis in this particular patient population has not been well studied, therapy should continue for at least as long as the patient remains mechanically ventilated.

## Nutritional Support

Cardiac surgery patients who develop significant postoperative complications are at risk for the development of malnutrition in the same way as other critically ill patients. The acute stress response to critical injury/illness includes the development of a catabolic state characterized by (1) increased glycogenolysis and gluconeogenesis (often with hyperglycemia and insulin resistance), (2) increased proteolysis and nitrogen wasting, and (3) alterations in micronutrients. The extent of muscle wasting and weight loss in the ICU is inversely correlated with long-term survival. Malnutrition is associated with a number of deleterious consequences, including infection, poor wound healing, the formation of decubitus ulcers, overgrowth of bacterial flora, and immune system dysfunction.

Although the presence of malnutrition is clearly associated with adverse outcome, the impact of nutritional support on outcome in the critically ill patient is more controversial. Data that specifically address the utility of nutritional support in cardiac surgery patients are nonexistent; one must

**TABLE 26-4: Comparison of Renal Replacement Therapy Modes**

| | Urea Clearance | CV Stability | Osmolar Stability | Fluid Balance | Cytokine Clearance |
|---|---|---|---|---|---|
| IHD | 200 mL/min<br>22 L/day (4 H × 3/week) | – | – | – | – |
| CVVHD | 25 mL/min<br>36 L/day | + | + | + | + |

CV, cardiovascular; CVVHD, continuous veno–veno hemodialysis; IHD, intermittent hemodialysis; –, disadvantage; +, advantage.

extrapolate from the general surgery literature. In one meta-analysis of randomized trials in patients who underwent general surgery, total parenteral nutrition did not change overall mortality but was associated with fewer major complications than standard care (i.e., oral diet and dextrose infusion). In surgical patients with protein–calorie malnutrition, parenteral nutrition reduced both mortality and infectious complications compared with standard care. However, enteral support is associated with an even lower risk of infectious complications than parenteral support and is therefore preferred if at all possible.[21]

## Glucose Management

Hyperglycemia has been shown to be deleterious to critically ill patients. Various studies have shown a direct relationship between hyperglycemia and infection, need for renal replacement therapy, ventilatory support, blood transfusion, and mortality. More specifically, in postoperative cardiac surgery patients, elevated blood glucose has been linked to an increased incidence of deep sternal wound infections, all-cause infection and sepsis, and mortality. High levels of serum epinephrine and cortisol contribute to this problem of hyperglycemia by producing a state of insulin resistance.

The initial data in postoperative open heart surgery patients, which showed benefit from the lowering of blood glucose, were in diabetics, wherein dramatic improvement in mortality as well as deep sternal wound infections occurred with intravenous insulin therapy. The target blood sugar in the population that benefited was 100 to 150 mg/dL. Subsequent data in a mixed medicine and surgery population in which over half were open heart surgery patients justified even tighter control, between 80 to 110 mg/dL. However, it now appears that the morbidity and mortality associated with the episodes of hypoglycemia associated with such tight control outweigh the benefits,[22] and thus current thoracic society recommendations are blood glucose targets of less than 180 mg/dL for the first two postoperative days, controlled with intravenous insulin infusion.

# INFECTION

Patients undergoing cardiac surgery are at risk for surgical site infections, as with any surgical patient population, and perioperative prophylactic antibiotics are recommended. A first- or second-generation cephalosporin should be given, unless allergic to penicillin, in which case vancomycin should be substituted. These antibiotics should be discontinued in less than 48 h to be compliant with the current guidelines of the Surgical Care Improvement Project.

## Sternal Wound Infections/Mediastinitis

Deep sternal wound infections occur in approximately 1 to 2 percent of patients after open heart surgery, although the literature cites incidences that vary from as low as 0.2 percent up to 8 percent. What is crucial about this particular infection is that the associated mortality can be as high as 50 percent. Furthermore, this complication occurs late, 1 to 2 weeks past surgery, often after discharge.

Risk factors for the development of sternal wound infections include diabetes, obesity, surgical reexploration (for bleeding), the use of the IMA, and prolonged postoperative ventilation and ICU stay. The classic signs and symptoms of mediastinitis are chest pain out of proportion to what should be experienced so many days from surgery, sternal instability, fever, and a significant leukocytosis. Effective therapy requires immediate and aggressive wound debridement with placement of vascularized tissue, muscle, and even omentum, in the anterior mediastinal space. On occasions, the sternum can be saved. Finally, appropriate and prolonged antibiotics are required, as guided by the intraoperative cultures that should always be obtained at the time of the initial mediastinal exploration.

## Venous Catheter Infections

The presence of central venous catheters in cardiac surgery patients is nearly universal. These catheters are useful for administering medications that cannot be safely given peripherally and for monitoring hemodynamic status. However, they are associated with the development of mechanical (pneumothorax, bleeding, venous thrombosis) and infectious complications that occur with an overall frequency of between 5 and 20 percent. Subclavian vein catheterization is associated with a lower complication rate (except for pneumothorax) than with the use of either the femoral or internal jugular vein; therefore, the subclavian site is preferred. Because the incidence of complications from central venous catheters is alarmingly high, an incidence that increases with time, the need for ongoing central venous access should be evaluated on a daily basis. All central venous catheters should be removed at the earliest possible time.

A variety of strategies to prevent infectious complications from central venous catheters have been tested, as demonstrated in Table 26-5.[23] In brief, full barrier protection (i.e., sterile gown and gloves, cap and mask, full-body sterile drape) during catheter insertion and skin preparation with chlorhexidine have proven efficacious in reducing catheter-related infectious complications and should be the standard of care. Antiseptic-coated catheters are effective at reducing infectious complications and are cost-effective when the hospital's rate of catheter-related bloodstream infection (CRBSI) is greater than 2 percent.

Routine scheduled replacement of catheters over a guidewire or placement at a new site does not decrease infectious complications and is associated with an increased risk of mechanical complications. Catheters should be replaced only when there is clinical suspicion of infection. An algorithm for the management of suspected catheter-related infection has been developed, but, briefly, a catheter-related infection should

**TABLE 26-5: Interventions to Prevent Infectious Complications of Central Venous Catheters**

| Type of Intervention | Rationale |
|---|---|
| Avoid scheduled routine catheter changes | Routine catheter changes to new sites do not decrease the risk of catheter-related bloodstream infections (CRBSI); routine rewiring of existing catheters is associated with a trend toward increased CRBSIs |
| Remove catheters as soon as they are not needed any more | Likelihood of colonization and CRBSIs increases over time |
| Use maximal sterile barrier precautions during insertion, including full gown, hat, mask, gloves for all personnel involved in the procedure, as well as full-length sterile drapes | Maximal sterile barrier equipment use reduces cost & infection rates |
| Use the subclavian venous site for catheter insertion | Subclavian catheterization shows the greatest reduction in risk of infection compared with internal jugular and femoral venous cannulation sites |
| Avoid antibiotic ointment applications to central venous insertion sites | Rates of colonization by fungi increased, growth of resistant bacteria encouraged, and infection risk not decreased |
| Disinfect catheter hubs | Hubs are common sites of catheter contamination |
| Use antimicrobial-impregnated catheters | Reduces the risk of CRBSIs, and also cost |

Adapted from McGee DC, Gould MK. Preventing complications of central venous catheterization. *N Engl J Med* 2003;348(12):1123–1133.

be suspected in any patient who has had a central venous catheter in place for 3 days or more and who displays evidence of infection without an identifiable source. If evidence of an exit-site infection is present on examination, the catheter should be removed and a new one placed at a new site. If the exit site is not clearly infected, the catheter should be exchanged over a guidewire and the intracutaneous portion sent for culture. If the catheter culture is positive, the indwelling catheter should be removed and a new one placed at a new site. If the catheter culture is negative, a catheter-related infection is unlikely.[23]

## Sepsis

Sepsis is a systemic response to infection that is defined by (1) a white blood cell count above 12,000, below 4000, or with more than 10 percent bands and (2) two or more of the following: temperature above 38.5°C or below 36.0°C, heart rate above 90 beats per min, respiratory rate above 20 breaths per min, or $PaCO_2$ below 32 mm Hg. Septic shock is defined as sepsis-induced hypotension (systolic BP less than 90 mm Hg or greater than 40 mm Hg reduction from baseline) or the requirement for vasopressors/inotropes in the face of evidence for organ hypoperfusion (e.g., altered mental status, oliguria, lactemia) despite adequate fluid resuscitation. Severe sepsis is associated with a mortality of 30 percent.

The key components of successful management are rapid, effective hemodynamic resuscitation and early administration of appropriate antibiotics for source control. In the emergency room setting, rapid institution of goal-directed therapy (fluids to maintain central venous pressure at 8 to 12 mm Hg, vasopressors to maintain MAP above 65, vasodilators to maintain MAP below 90, and red cell transfusion and/or dobutamine to achieve mixed venous $O_2$ saturation above 70 percent) in patients presenting with sepsis improved in-hospital survival from 30 to 45 percent.[24] These findings contrast with older studies that failed to show a benefit of hemodynamic optimization strategies, but the older studies began goal-directed therapy much later in the septic process. Early, rapid resuscitation with goal-directed therapy appears to be vital to an improved outcome.

The Surviving Sepsis Campaign (SSC) was an effort to consolidate evidence-based best practices identified to reduce the significant mortality and morbidity in patients with sepsis and septic shock. Following these management guidelines, the IHI and the Volunteer Hospitals Association (VHA) put forth a series of interventions that would work synergistically to improve outcomes in sepsis and septic shock. These were organized into the sepsis resuscitation bundle, to be implemented within the first 6 h after diagnosis of severe sepsis, and the sepsis management bundle, to be initiated simultaneously but to be completed within the first 24 h after diagnosis. Although these hopefully do not routinely need to be addressed in the postoperative care of cardiac surgical patients, a thorough knowledge of the sepsis bundles is essential to their care.

Since the publication of the initial SSC guidelines in 2001, updated as recently as 2008, multiple studies have demonstrated significant decreases in mortality and morbidity in septic patients with the implementation of the sepsis bundle. However, it must be stressed that bundles, in and of themselves, are not the answer to managing septic shock. Instead, they serve as tools to implement evidence-based clinical practice guidelines, and encourage a multidisciplinary team-based approach to the complex management of these critical patients.

Regarding steroids in the treatment of septic shock, steroids (hydrocortisone 50 mg q 6 h) improve survival and reduced the need for vasopressor therapy in patients with relative adrenal insufficiency (defined as failure to increase serum cortisol by at least 10 μg/dL during the ACTH stimulation test), but no benefit has been observed in patients without adrenal insufficiency.[26]

## CHECKLISTS AND CLINICAL PATHWAYS IN CARDIAC SURGERY

Checklists have been part of the standard of care in the aviation industry for many years. The crucial role they played in the Michigan Keystone project that dramatically minimized the incidence of CRBSIs in ICU patients has led to their introduction into the field of critical care.[27,28] Critical care and perioperative care have become increasingly complicated, and without utilization of external aids, reliance on individual, physician performance will lead to continued, preventable errors in care and patient management. The creation of checklists that are task-specific can be a cumbersome job, but if undertaken thoughtfully and with an inbuilt plasticity, it can have lasting effects on outcomes. The underlying premise involves the simplification of a process, procedure, or intervention in order to make that process safer. However, simply creating a checklist and handing it to ICU or surgical staff to implement is doomed to failure; the engagement and buy-in of those who will be actively involved in implementing such a tool is crucial to its success. Surgeons are just now beginning to implement tools such as checklists into their practices to attempt to improve outcomes in the perioperative care of their patients (also see the UK Society for Cardiothoracic Surgery's website (www.scts.org)).

Similarly, "critical pathways," defined as "problem-specific protocols designed to move patients along a designated set of intermediate then long-term goals in a timely fashion" have been developed. In cardiac surgery, this is done in an attempt to "fast-track" straightforward cardiac surgery patients toward goals such as earlier extubation, more rapid mobilization, and removal of invasive lines and devices as soon as medically allowed. Many of these protocols use daily checklists that differ based on the postoperative day, and make allowance for the individual variations of each patient, but overall, aim to keep patients "on-track" to early (but safe) discharge.

The common theme to the successful implementation of these types of patient-safety, quality assurance tools is a multidisciplinary approach to their creation and use, with a culture of openness to improvement and revision of the process. In addition, inculcating in the work environment the expectation of performance improvement via measurement of goals, with constant and appropriate feedback, is required if quality is to be maintained. The successful physicians (medical students, residents, and attendings) have made personal checklists for years. Formalizing them and making them a part of the entire caregiving team is now becoming the long overdue norm.

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## POSTOPERATIVE MANAGEMENT OF THE CARDIAC SURGICAL PATIENT BOARD REVIEW QUESTIONS (CHAPTER 26)

1. An 87-year-old male with an ejection fraction of 35 percent undergoes an uneventful triple-vessel CABG. He is extubated within 6 h after surgery, and transfers to the step-down unit the next day on aspirin, furosemide, and potassium with a mean blood pressure of 75. Two days later, he is transferred back to the ICU reintubated, hypotensive, in atrial fibrillation with a rapid ventricular response at a rate of 200 bpm. He is successfully cardioverted, and in sinus rhythm at 90, his blood pressure stabilizes. His magnesium and potassium were 2.1 and 4.2 mEq/L, respectively. His oxygen saturation had been 92 percent on room air when he developed atrial fibrillation, and rose with nasal oxygen. His EKG showed no evidence of ischemia. How could this complication have potentially been prevented?
   A. Used nasal oxygen until room air sats were >95 percent on room air, not 92 percent
   B. Administered amiodarone postoperatively
   C. Prescribed only thick liquids to prevent aspiration
   D. Kept this elderly patient in the ICU longer for more intense monitoring
   E. Prescribed warfarin postoperatively

2. A 24-year-old male undergoes a left ventricular (LV) septalmyectomy for hypertrophic obstructive cardiomyopathy (HOCM). He separates easily from bypass with a CVP of 9, and returns to the cardiac ICU in normal sinus rhythm at a rate of 90, with a left bundle branch block (LBBB) and atrial and ventricular epicardial pacing wires in place. During the first hour of his postoperative course, his blood pressure is very labile, with systolic pressures ranging from 70 to 180, and a CVP of 3. What should be the course of action in the immediate postoperative period to stabilize this patient?
   A. Initiation of nitroprusside as an afterload reducing agent
   B. DDD pace at 100 bpm
   C. Add β-blocker to minimize stress on the aortic suture line
   D. Volume resuscitation
   E. Add milrinone at 0.3 μg/kg/min

3. The likelihood of requiring tracheostomy for ventilator-dependent respiratory failure is greatest in which of the following patients?
   A. A 30-year-old Marfan patient after an emergency aortic root replacement for an acute ascending aortic dissection
   B. A 70-year-old patient with baseline room air hypoxia on home oxygen but without evidence of $CO_2$ retention s/p semi-urgent 4-vessel CABG in the setting of a NSTEMI
   C. A 70-year-old 40 pack-year smoker after aortic valve surgery extubated intraoperatively who required reintubation upon arrival to the ICU for a severe respiratory acidosis with somnolence
   D. A 80-year-old 100 pack-year smoker who underwent a redo sternotomy for coronary bypass and rereplacement of his mitral valve, with a bypass time of 270 min and intraoperative IABP placement due to initial inability to separate from CPB
   E. A 72-year-old patient with a juvenile history of Guillain–Barré syndrome requiring a tracheostomy at the time, now s/p 3-vessel CABG

4. A 75-year-old man undergoes a 2-vessel CABG with a LIMA–LAD arterial graft and a saphenous vein graft to his obtuse marginal artery. His 90 percent proximal RCA stenosis is unable to be revascularized due to a poor distal vessel. Two hours after surgery, the EKG shows inferior ST segment elevation. He also has bradycardia with first degree heart block and a rising CVP with no change in the PAD. On epinephrine at 0.15 μg/kg·min and AV pacing at 90, the mean blood pressure is 55 mm Hg, the cardiac index is 1.8 L/min/$m^2$, and the mixed venous oxygen saturation is 48 percent. The next appropriate step in management is:
   A. Immediately place an intra-aortic balloon pump (IABP)
   B. Undergo urgent cardiac catheterization with an attempt to stent the RCA
   C. Add dobutamine to improve cardiac output
   D. Stop pacing and allow patient to have his own AV sequential rhythm
   E. Start amiodarone to prevent ischemia-induced atrial or ventricular arrhythmias

5. Efforts to reduce nosocomial infections in patients after open heart surgery should include which of the following:
   A. Routine central venous catheter changes every 72 h to minimize the risk of catheter-related bloodstream infections
   B. Continuation of antibiotics as long as the patient is intubated and mechanically ventilated to prevent ventilator-associated pneumonia
   C. Removal of the urinary catheter as soon as the patient is extubated, stable, and mobile
   D. Avoidance of providing enteral or parenteral nutrition for patients in critical condition for greater than 5 days
   E. The use of blood glucose control via an insulin sliding scale only after the patient is extubated and eating a regular diet

## ANSWERS

1. **Answer: B.** Prophylactic amiodarone may reduce the incidence of postoperative atrial fibrillation. Postoperative atrial fibrillation has many etiologies, including hypoxia, ischemia, hypomagnesemia, and hypokalemia. Aspiration of liquids in an 87-year-old man resulting in hypoxia-induced atrial fibrillation is unlikely give the patient's stable respiratory status. Prolonged observation in the ICU with more intense monitoring does not prevent arrhythmias. Prophylactic anticoagulation with warfarin has no role in the prevention of postoperative atrial fibrillation. Atrial fibrillation develops in approximately 30 percent of CABG patients, most commonly on the second postoperative day. Although a β-blocker diminishes this incidence as effectively as amiodarone, in this patient with borderline blood pressure, amiodarone is the drug of choice for atrial fibrillation prophylaxis.
2. **Answer: D.** HOCM patients, by the nature of their pathophysiology, demonstrate hypertrophy of their entire left ventricle, not just the septum, and are therefore exquisitely sensitive to preload to maintain an adequate stroke volume. Afterload reducers such as nitroprusside or nicardipine may reduce blood pressure when hypertensive, but will also produce vasodilation, exacerbating the hypotension. AV pacing in a DDD mode at 100 compared to the patient's intrinsic rate of 90 will not increase the patient's cardiac output significantly and will not affect the lability of this patient's blood pressure. β-blockers in the face of LBBB might lead to heart block at this early time period and will exacerbate the hypotension. Milrinone will increase contractility, but in a noncompliant, thick, poorly filled ventricle, might lead to a functional subaortic obstruction, despite its surgical correction. This young, otherwise healthy 24-year old should be aggressively volume resuscitated with crystalloid to provide the hypertrophied LV with adequate preload.
3. **Answer: D.** The incidence of tracheostomy after open heart surgery is less than 2 percent, and the major risk factors include preexisting pulmonary dysfunction and prolonged cardiopulmonary bypass time. The young patient with Marfan syndrome should have no difficulty with extubation, despite the emergent nature of his surgery as long as there is no cerebral ischemic injury. In the chronically hypoxic patient, although oxygenation might be difficult early in the postoperative period, ventilation should be manageable, and current noninvasive techniques to increase the inspired oxygen concentration should allow extubation. Failure of intraoperative or early extubation is most probably due to weakness and residual anesthesia-induced insensitivity to hypercarbia, and should not lead to a prolonged intubation. In patients with a remote history of Guillain–Barré syndrome, residual muscular weakness should not be an issue.
4. **Answer: A.** Placement of an intra-aortic balloon pump (IABP) will improve the hemodynamics by augmenting diastolic blood pressure. This will, in turn, increase coronary perfusion, decrease aortic systolic pressure (a measure of LV afterload), and decrease LV end-diastolic pressure (a measure of preload). The end result is a decrease in myocardial oxygen demand, which should support the patient's hemodynamics during this acute inferior infarction. Although cardiac catheterization is always an option to consider in order to percutaneously revascularize the RCA, this patient will benefit from immediate mechanical support. Dobutamine may exacerbate the hypotension and increase myocardial work. Cessations of pacing and amiodarone have no role in the therapy of ventricular failure with shock.
5. **Answer: C.** Removal of the urinary catheter as soon as the patient is extubated, stable, and mobile. Urinary tract infections are the most common nosocomial infection, and the incidence is directly related to duration of the indwelling bladder catheter. Sterile barrier precautions at the time of insertion, along with timely removal of central venous catheters (not routine replacement of such catheters), diminishes the incidence of central venous line associated blood stream infections. Prolonged antibiotics are ineffective in preventing ventilator-associated pneumonia. Early, aggressive maintenance of nutrition and an anabolic state is beneficial in reducing postoperative morbidity, as is the prevention of hyperglycemia, without undue delay.

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# Primary Coronary Artery Bypass Surgery

*G.D. Rushing*
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**KEY CONCEPTS**

- Epidemiology
  - Affecting more than 1.5 million Americans annually, coronary artery disease is the most common form of heart disease, and its complications are the leading cause of death in both men and women.
- Pathophysiology
  - Coronary artery disease is generally caused by atherosclerotic luminal narrowing, resulting in insufficient coronary blood flow to the myocardium. The process consists of subintimal atheroma deposition, leading to arterial luminal stenosis or occlusion and wall thickening.
- Clinical features
  - Typically, significant coronary atherosclerosis becomes manifest as angina, but it can also present with anginal-equivalent symptoms, including dyspnea, dizziness, syncope, and pulmonary edema. Malignant coronary disease leading to ischemic cardiomyopathy is associated with congestive symptoms. Identified factors that contribute to severe atherosclerotic coronary artery disease include obesity, hypercholesterolemia, obesity, diabetes, tobacco use, and sedentary lifestyle.
- Diagnostics
  - Twelve-lead electrocardiography is initially used to diagnose myocardial ischemia. Further investigation consists of exercise stress testing, evaluation of myocardial enzymes (i.e., CPK-MB, troponin), echocardiography, and coronary angiography.
- Treatment
  - Initial medical management of acute myocardial ischemia consists of beta blockade, nitrates, antiplatelet therapy, and supplemental oxygen. After precise delineation of coronary arteriopathy, definitive treatment consists of coronary artery bypass grafting (CABG) or percutaneous angioplasty and stenting.
- Outcomes/prognosis
  - CABG carries an overall mortality of about 3 percent; elective primary coronary bypass carries a mortality rate of approximately 1.7 percent. Complications associated with CABG include renal failure, neurologic injury, heart failure, hemorrhage, respiratory failure, and renal dysfunction. Overall, CABG achieves excellent outcomes with respect to anginal relief and resumption of normal activities. In general, completeness and durability of revascularization is superior with surgical revascularization versus percutaneous interventions.

## INTRODUCTION

Coronary artery disease represents the most common cause of insufficient oxygen delivery to the myocardium, referred to as myocardial ischemia. Understanding the pathophysiology of arterial disease with subintimal atheroma and plaque formation has been a breakthrough of modern medicine. Even with our advanced understanding of heart disease, it remains the most common cause of death for Americans. Cardiovascular disease claims more lives (men and women) than cancer, trauma, and pulmonary disease combined.[1]

The first coronary artery bypass grafting (CABG) operation, using saphenous vein conduit, was performed by Dr. David Sabiston at Johns Hopkins Hospital in 1962 and has evolved into the "gold standard" therapy for patients with multivessel coronary artery disease. Despite advances in percutaneous interventional techniques, CABG remains among the most frequently performed operations in the

United States, associated with approximately US$50 billion in annual health care expenditures.

## NORMAL CORONARY ANATOMY AND PHYSIOLOGY

The right and left coronary arteries originate from the ascending aorta behind their respective aortic valve leaflets, usually in the upper third of the sinuses of Valsalva.[2] By convention, the artery that supplies the posterior descending artery (PDA) determines the coronary *dominance*. The coronary circulation is classified as "right dominant" if the PDA is supplied by the right coronary artery and as "left dominant," when supplied by the left circumflex artery. Occasionally, the PDA is supplied by both the left and the right coronary circulation and is therefore classified as "co-dominant." The coronary circulation is *right dominant* in 85 to 90 percent of normal individuals. This delineation is important when evaluating patients for CABG.

The right coronary artery is usually a singular vessel coursing down the right atrioventricular groove, supplying the anterior right atrial and sinoatrial nodal arteries. It continues over the acute margin of the heart, dividing into the right posterior descending and right posterolateral segmental arteries, perfusing the atrioventricular node and posterior wall of the left ventricle.

The left main coronary artery courses for a distance of 10 to 20 mm from the left sinus of Valsalva between the pulmonary trunk and left atrial appendage. It bifurcates into the left anterior descending (LAD) and circumflex coronary arteries near the left atrioventricular groove. The LAD traverses the anterior interventricular groove toward the apex of the heart, giving off diagonal, septal perforating, and right ventricular branches before terminating at the apex. Occasionally, in 10 to 15 percent of normal individuals, the LAD may collateralize with the PDA or replace it to supply the posterior interventricular groove. The diagonal branches supply the anterolateral wall of the left ventricle. The first diagonal branch may occasionally originate directly from the left main coronary artery and is then referred to as the ramus intermedius coronary artery. The septal perforators supply the anterior two-thirds of the ventricular septum, extending perpendicularly from the LAD. The right ventricular branches supply the anterior surface of the right ventricle.

The circumflex coronary artery courses along the left atrioventricular groove, giving off obtuse marginal branches to supply the lateral wall of the left ventricle, the left atrium, and the posteromedial papillary muscle. Occasionally, the sinus node artery is supplied from the proximal circumflex artery. In most patients, the circumflex coronary artery terminates near the obtuse margin of the left ventricle; in the remaining patients, (i.e., *left dominance*), it may continue and give rise to the posterior descending coronary artery.

Coronary blood flow is regulated by the oxygen demands of the heart.[3] Oxygen stores in the heart are minimal with extraction from the coronary blood flow at near maximal levels (70 percent) under a resting physiologic state. Due to this maximal oxygen extraction, when oxygen demands increase, as in exercise, a majority of oxygen delivery must come from increasing blood flow. Changes in myocardial oxygen requirements bring about a multitude of mechanisms to increase oxygen delivery. The major resistance vessels where these mechanisms are located constitute the arterioles and rich network of capillaries that form interregional collaterals. Myocardial blood flow is under complex regulation by a compilation of metabolic, neurogenic, and hormonal mechanisms.

Adenosine is the primary metabolite of myocyte activity regulating coronary blood flow via $A_2$ receptor-induced smooth muscle relaxation. ATP sensitive $K^+$ channels, hypoxia, and acidosis are other potent metabolic regulators of coronary blood flow. Neurogenic regulation occurs directly and indirectly via sympathetic and vagal innervations. Direct innervations of larger conductance vessels and indirect innervations of smaller resistance arterioles with release of norepinephrine cause vasoconstriction (via $\alpha_1$ receptors) and vasodilatation (via $\beta_2$ receptors). Vagal release of acetylcholine primarily causes vasodilatation of conductance vessels. Hormonal control of coronary blood flow occurs mainly by local endothelial derived substances such as nitric oxide (vasodilatation) and endothelin-1 (vasoconstriction). However, nonlocal paracrine control of coronary blood flow can be influenced by platelet derived mediators such as thromboxane $A_2$ (vasoconstriction), adenosine diphosphate (vasodilatation) and serotonin (both).

Given the near obligatory aerobic physiology of the heart, metabolic, neurologic, and hormonal mechanisms quickly react to increase coronary blood supply and adequate oxygen delivery. With this autoregulatory system, the heart is particularly vulnerable to occlusive arterial disease.

## PATHOPHYSIOLOGY OF MYOCARDIAL ISCHEMIA/INFARCTION

Coronary atherosclerosis is a slow, complex disease process that typically starts in childhood and often progresses with age. Its precise cause still remains incompletely understood. The "Response to Injury" hypothesis was put forth by Ross and Glomset who combined proposals made initially by Virchow and Rokitansky with more modern knowledge of molecular and cellular biology.[4] Infiltration of small lipoprotein particles accumulate in the vessel intima, starting in childhood. Binding of these lipoproteins to proteoglycan make these areas more prone to endothelial injury.[5] Mechanisms of endothelial injury are thought to include: turbulent flow, infectious and immunologic factors, and noxious chemicals. Once leukocytes extravasate into the intima, they become lipid-laden macrophages and multiply. With the release of various chemotactic growth factors and vasoconstrictors such as thromboxane $A_2$, migration and proliferation of smooth muscle cells results in the accumulation of collagen, elastic fibers, proteoglycan, calcium,

complex carbohydrates, and other connective tissues in the intimal and subintimal areas.[6] This deposition progresses to become an atherosclerotic plaque. Within an atherosclerotic plaque, angiogenesis of newly formed small vessels can suddenly bleed, causing plaque hemorrhage and rupture, which can worsen the degree of stenosis and precipitate a myocardial infarction.[7] It is believed that most acute myocardial infarctions result from acute thrombotic occlusion.

Coronary atherosclerosis usually involves the proximal portions of larger epicardial coronary arteries, especially at or just beyond branching sites. Therefore, stenoses of the LAD, circumflex, and right coronary arteries often involve the first of the secondary branchings (i.e., first diagonal, obtuse marginal, and posterior descending branches). When the disease is more severe, origins and main trunks may be involved. The left main coronary artery is significantly diseased in 10 to 20 percent of patients. Diffuse distal disease severe enough to render a coronary artery unsuitable for bypass grafting is relatively uncommon.

With coronary artery disease, myocardial ischemia and necrosis occur when coronary blood flow, impaired by atherosclerotic stenosis, is insufficient to meet oxygen demand. Because the heart has virtually no reserve stores of oxygen and relies entirely on aerobic metabolism, its high rate of energy expenditure results in a sudden, striking decline of oxygen tension and left ventricular functional impairment within seconds of coronary occlusion. Coronary occlusion can cause myocardial ischemia in as little as 60s, and depressed function, or myocardial stunning, in less than 20 min.[8] The subendocardium is most vulnerable to myocardial ischemia because its collateral blood flow is lowest and oxygen consumption highest.[9] Thus, myocardial necrosis progresses toward the epicardium with continued ischemia and is accelerated when there is little collateral flow, marked arterial hypotension (e.g., cardiogenic shock), and elevated oxygen demand caused by inotropic stimulation or tachycardias. Thus blood pressure control and the prevention of tachyarrhythmias are vital during the early postinfarction interval to limit the spread of myocardial damage. The recognition of this time-dependent progression of infarct and the conditions necessary for functional recovery of salvaged myocardium constitute the basis for rapid reperfusion interventions, including thrombolysis and angioplasty. Multiple randomized trials have demonstrated that fibrinolytic therapy within 1 h hour of symptoms remarkably decreases the 30-day mortality of acute myocardial infarction.[10]

Hypercholesterolemia and other conventional risk factors may precipitate or accelerate the process of coronary atherosclerosis. The identified controllable risk factors are:

- Hypercholesterolemia (especially low-density lipoprotein >100 mg/dL)
- Smoking or exposure to tobacco smoke
- High blood pressure
- Diabetes mellitus
- Obesity
- Physical inactivity

Although global risk assessment models like Framingham are useful, up to 20 percent of patients with coronary artery disease have no conventional risk factors and up to 50 percent only have one risk factor. In light of this, additional risk factors for coronary atherosclerosis are being investigated and tested, including C-reactive protein, lipoprotein A, fibrinogen, and homocysteine.

## CLINICAL CORONARY SYNDROMES

### Stable Angina

*Angina pectoris* is the development of chest discomfort or pain with exertion that ceases within 5 to 15 min of rest, or administration of sublingual nitroglycerin. It is typically described as a substernal heavy, dull, or crushing pain with frequent radiation to the left shoulder, arm, and/or neck. Other sensations are more vague, including pressure, numbness, and burning. It is not an inevitable symptom, nor does its absence indicate freedom from coronary artery disease; however, it does signify the presence of reversible myocardial ischemia without cellular necrosis. Decreased myocardial oxygen supply or increased myocardial oxygen demand leads to symptoms. Since angina results from a reduction in coronary flow reserve, the greater the reduction, the more severe the angina. Several classification systems exist, however the Canadian Cardiovascular Society Functional classification has become the most accepted.[11] The severity of angina is categorized into the following four categories:

- Class 1: Angina occurring with strenuous activity. There is no limitation to ordinary activity.
- Class 2: Angina occurring with fast-paced walking or walking up an incline or stairs. There is only slight limitation to ordinary activity.
- Class 3: Angina occurring when walking less than two blocks on level ground or climbing one flight of stairs. There is significant limitation to ordinary activity.
- Class 4: Angina occurring with mild activity. May occur at rest but lasts less than 15 min (beyond which the angina is unstable). There is inability to carry out mild activity.

The clinical presentation of patients with angina varies considerably. Part of this is explained by *fixed threshold* versus *variable threshold* angina. Fixed threshold angina is due to increased myocardial oxygen demands. The level of exertion to precipitate oxygen debt resulting in angina is relatively "fixed" (two flights of stairs). Variable threshold angina includes dynamic vasoconstriction as an important part of decreased oxygen supply, not just atherosclerotic narrowing of epicardial coronary vessels. These patients are noted to have "good days" and "bad days" as their level of exertion that precipitates angina is varied.

Furthermore, as chest pain in general tends to be nonspecific, the differential diagnosis is broad and includes gastrointestinal reflux, biliary colic, peptic ulcer disease, aortic dissection, esophageal disorders, lower respiratory

tract infection, pneumonitis, and a variety of musculoskeletal discomforts. Once other differential diagnoses are ruled out, evaluation with electrocardiography (ECG), exercise or stress testing, and myocardial enzyme levels are necessary to confirm the diagnosis of myocardial ischemia. In general, patients with class 1 and 2 stable angina can be managed medically with coronary angiography as an option following provocative testing for ischemia. Coronary angiography is recommended for patients with class 3 and 4 angina.

## Atypical Anginal Equivalents

Anginal equivalents are described as symptoms of myocardial ischemia other than angina. These symptoms include dyspnea, fatigue, syncope, dizziness, and pulmonary edema. These symptoms are common in the elderly and often due to left ventricular systolic or diastolic dysfunction whenever the myocardium becomes ischemic under stress. Furthermore, a small number of patients exhibit "silent" or asymptomatic ischemia that can be discovered only by continuous ECG monitoring. Nocturnal angina should raise the suspicion of sleep apnea.

## Acute Coronary Syndromes

Acute coronary syndromes are a spectrum of symptomatic and prognostic worsening of coronary artery disease. Included in this spectrum are unstable angina, non-ST-segment elevation myocardial infarction, and Prinzmetal angina. They are predominantly due to plaque rupture and variable thrombosis/occlusion of the coronary arterial system. Other proposed mechanisms of acute coronary syndrome include coronary spasm as seen in Prinzmetal angina and secondary causes of decreased myocardial oxygen demand such as anemia. This clinical situation remains reversible but tends to recur either as further episodes of unstable angina or a fulminant acute myocardial infarction.

Unstable angina is defined as angina pectoris pain (or equivalent) that includes at least one of the following three characteristics: (1) lasting greater than 20 min if not interrupted by medical intervention, (2) being severe and recent (within 1 month of onset), and (3) presents with crescendo patterns (being more painful, longer duration, or increasing frequency). Furthermore, unstable angina can be categorized according to the clinical presentation of each ischemic event: primary unstable angina, secondary angina (i.e., anemia), and postinfarct angina (less than two weeks after myocardial infarction).

Prinzmetal angina is a variant that causes pain and ST-segment elevation at rest. The proposed mechanism has been increased coronary vasomotor tone or spasm. No precise mechanism has been elucidated, but mutations in genes responsible for the production of nitric oxide and endothelium-derived relaxing factors may play a role.[12] The crucial element to diagnose Prinzmetal variant angina is the detection of episodic ST-segment elevation with pain. ST-segment deviations may be present in any leads. Treatment for Prinzmetal variant angina includes smoking cessation, short acting and long acting nitrates, and calcium agonists. Patients with ventricular fibrillation associated with Prinzmetal variant angina may require automatic implantable cardiodefibrillator placement.[13]

Patients presenting with acute coronary syndrome are evaluated with clinical history, ECG examination, and cardiac biomarker (troponin) level measurement. These patients are treated depending on their risk stratification. Those with low risk are treated with an antithrombotic agent such as aspirin, clopidogrel, or an antithrombin, along with β-blockers and nitrates. Patients with positive troponin levels or ST-segment changes (high risk) are treated with the addition of GP IIb/IIIa inhibition as well as coronary angiography with percutaneous coronary intervention (PCI) or CABG if necessary. A calcium agonist is added for patients with Prinzmetal variant angina. Several trials demonstrate that early intervention in high-risk unstable angina patients results in decreasing mortality, myocardial infarction, and rehospitalization rates.[14]

## Acute Myocardial Infarction

Prolonged myocardial ischemia without reperfusion ultimately leads to irreversible cellular necrosis and myocardial infarction. Most acute myocardial infarctions result from subtotal or total coronary artery occlusion by a thrombus associated with acute rupture of an atherosclerotic plaque. Although the acutely occluded coronary artery often was not previously severely stenotic, the mere presence of significant coronary artery disease clearly increases the risk for acute myocardial infarction. For example, patients with severe proximal LAD coronary lesions are particularly prone to suffer acute and often fatal myocardial infarctions. Increased numbers of coronary arteries with stenotic disease also lead to higher probabilities of acute myocardial infarction.

Following an infarction, the location of the coronary arterial occlusion, presence of other diseased vessels, and extent of collateral perfusion will determine the extent of myocardial injury in the early period. Additional detrimental effects of postinfarct arrhythmias, hypotension, left ventricular distention, and increased wall stress can further reduce the viability of borderline regions and increase the ultimate infarct size.

According to the American Heart Association, the updated universal definition of myocardial infarction is[15]: Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia;
- ECG changes indicative of new ischemia [new ST–T changes or new left bundle branch block (LBBB)];
- Development of pathologic Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Typically, patients present with a sudden onset of severe chest pain or their anginal equivalent that is not relieved by rest or sublingual nitroglycerin. Often, there is associated shortness of breath, nausea, diaphoresis, and general malaise. Subendocardial or nontransmural infarctions usually demonstrate new ST-segmental depressions and T-wave inversions on the 12-lead ECG. As the infarction progresses, ST segments may become elevated and later evolve into Q waves that indicate a transmural infarct.

Since less than 25 percent of patients admitted to the hospital with ischemic-type chest discomfort are subsequently diagnosed as having had an acute myocardial infarction and about half of all patients with acute myocardial infarction do not exhibit diagnostic ST-segment changes, myocardial enzyme markers play an essential role in establishing the diagnosis. The classic myocardial creatine kinase isoenzyme CK-MB, which appears within hours after injury and peaks at 8 to 24 h after infarction, lacks sufficient sensitivity and specificity but remains an efficient means of early detection. Levels of troponin, with its cardiac specific subunits I and C, are more sensitive and specific for myocardial infarction. Furthermore, because troponin release is stoichiometrically correlated with the amount of myocardial necrosis, these enzymes can also be used to estimate infarct size and prognosis. Since serum troponin levels may present up to 14 days after infarction, detection of recurrent acute infarction requires concomitant CK-MB measurements.

### Chronic Ischemic Heart Disease

Some patients with progressive coronary artery disease suffer from chronic, recurrent myocardial ischemic episodes rather than a single devastating infarction. Consequently, these patients develop symptoms of chronic ischemic cardiomyopathy and congestive heart failure (shortness of breath and peripheral edema). Myocardial ischemia impairs left ventricular function and increases the workload on normal myocardium. Increasing areas of dyskinesis or akinesis from repeated insults results in greater reduction of both systolic and diastolic function. Often, these patients exhibit symptoms of heart failure associated with recurrent myocardial ischemia. Furthermore, right ventricular function can also be expected to be impaired in patients with chronic ischemic heart disease. This can be due to occlusive disease of the right coronary artery, pulmonary arterial hypertension, dyskinesis of the ventricular septum, and left ventricular dilatation.

There is a great deal of physiologic and functional variability among patients with depressed ventricular function from chronic ischemic heart disease. Therefore preoperative prediction of the efficacy of surgical intervention can be difficult. Some patients have moderately increased left ventricular end-diastolic pressures and reduced exercise capacity but minimal cardiomegaly. Although these patients often have marked ischemic dysfunction, revascularization is indicated to rescue or protect viable myocardium and improve functional capacities. In some cases, poor left ventricular function is due to myocardial "hibernation" or "stunning" and therefore may benefit from revascularization. In general, patients with recurrent heart failure and reversible ischemic episodes are likely to improve after CABG.

In some patients, chronic myocardial ischemia leads to ischemic cardiomyopathy. This is signified clinically by moderate-to-severe cardiomegaly, reduced cardiac output, significantly elevated right-sided venous pressures, hepatomegaly, ascites, and peripheral edema. The advanced left ventricular dysfunction is the result of extensive myocardial scarring due to a sustained reduction in coronary perfusion. These patients tend to have diffuse small vessel coronary disease and are therefore not expected to benefit from revascularization.

## INDICATIONS FOR CORONARY ARTERY BYPASS GRAFTING

With the advent of coronary stent technology, indications for coronary artery bypass surgery are evolving. Indications for coronary artery bypass surgery are predicated on improving the patient's quality of life (i.e., relief of symptoms, increased exercise tolerance, prolonged survival). Based on an extensive review of the literature, a joint task force from the American College of Cardiology and American Heart Association revised the original 1991 guidelines for coronary artery bypass surgery in 2004 (Table 27-1).[16] Nominally, based on several studies showing improved myocardial function following operative reperfusion, emergency surgical revascularization is generally preferred over medical/percutaneous intervention after acute myocardial infarction. There is general agreement that CABG provides a survival advantage as compared with medical therapy in patients with (1) left main stenosis, (2) three-vessel disease, (3) two-vessel disease with proximal LAD stenosis, (4) impaired left ventricular function, and (5) severe ischemia and multivessel disease. Percutaneous interventions are now available, which provide improved symptoms over medical therapy alone; however, survival advantages have not been seen.[17,18]

Several clinical trials have recently compared revascularization between percutaneous and surgical methods. Data are now being collected on the utilization of drug eluting stents (DES), which appear to be associated with lower rates of reintervention than traditional bare metal stents. CABG clearly possesses an advantage over any type of coronary stent if reintervention is required. A recent database study compared CABG and DES in patients with either two- or three-vessel coronary artery disease. Evaluation of New York State Department of Health databases in these patients showed that those who underwent CABG experienced lower mortality, myocardial infarction, and revascularization rates than those who underwent DES placement.[19] The Arterial Revascularization Therapies Study II (ARTS II) also evaluated DES in patients with multivessel coronary artery disease.[20] Rates of major adverse cardiac and cerebrovascular events (MACCE) were observed in 27 percent of patients

## TABLE 27-1: American College of Cardiology/American Heart Association Guidelines for Coronary Artery Bypass Graft Surgery: Indications

**Asymptomatic or mild angina**

**Class I**

1. CABG should be performed in patients with asymptomatic or mild angina who have significant left main coronary artery stenosis. (*Level of Evidence: A*)
2. CABG should be performed in patients with asymptomatic or mild angina who have left main equivalent: significant (greater than or equal to 70%) stenosis of the proximal LAD and proximal left circumflex artery. (*Level of Evidence: A*)
3. CABG is useful in patients with asymptomatic ischemia or mild angina who have three-vessel disease. (Survival benefit is greater in patients with abnormal LV function; e.g., EF less than 0.50 and/or large areas of demonstrable myocardial ischemia.) (*Level of Evidence: C*)

**Class IIa**

CABG can be beneficial for patients with asymptomatic or mild angina who have proximal LAD stenosis with one- or two-vessel disease. (This recommendation becomes a class I if extensive ischemia is documented by noninvasive study and/or LVEF is less than 0.50.) (*Level of Evidence: A*)

**Class IIb**

CABG may be considered for patients with asymptomatic or mild angina who have one- or two-vessel disease not involving the proximal LAD (If a large area of viable myocardium and high-risk criteria are met on noninvasive testing, this recommendation becomes class I). (*Level of Evidence: B*)

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**Stable angina**

**Class I**

1. CABG is recommended for patients with stable angina who have significant left main coronary artery stenosis. (*Level of Evidence: A*)
2. CABG is recommended for patients with stable angina who have left main equivalent: Significant (greater than or equal to 70%) stenosis of the proximal LAD and proximal left circumflex artery. (*Level of Evidence: A*)
3. CABG is recommended for patients with stable angina who have three-vessel disease. (Survival benefit is greater when LVEF is less than 0.50.) (*Level of Evidence: A*)
4. CABG is recommended in patients with stable angina who have two-vessel disease with significant proximal LAD stenosis and either EF less than 0.50 or demonstrable ischemia on noninvasive testing. (*Level of Evidence: A*)
5. CABG is beneficial for patients with stable angina who have one- or two-vessel CAD without significant proximal LAD stenosis but with a large area of viable myocardium and high-risk criteria on noninvasive testing. (*Level of Evidence: B*)
6. CABG is beneficial for patients with stable angina who have developed disabling angina despite maximal noninvasive therapy, when surgery can be performed with acceptable risk. If angina is not typical, objective evidence of ischemia should be obtained. (*Level of Evidence: B*)

**Class IIa**

1. CABG is reasonable in patients with stable angina who have proximal LAD stenosis with one-vessel disease. (This recommendation becomes class I if extensive ischemia is documented by noninvasive study and/or LVEF is less than 0.50). (*Level of Evidence: A*)
2. CABG may be useful for patients with stable angina who have one- or two-vessel CAD without significant proximal LAD stenosis but who have a moderate area of viable myocardium and demonstrable ischemia on noninvasive testing. (*Level of Evidence: B*)

**Class III**

1. CABG is not recommended for patients with stable angina who have one- or two-vessel disease not involving significant proximal LAD stenosis, patients who have mild symptoms that are unlikely due to myocardial ischemia, or patients who have not received an adequate trial of medical therapy and
   a. have only a small area of viable myocardium or (*Level of Evidence: B*)
   b. have no demonstrable ischemia on noninvasive testing. (*Level of Evidence: B*)
2. CABG is not recommended for patients with stable angina who have borderline coronary stenoses (50–60% diameter in locations other than the left main coronary artery) and no demonstrable ischemia on noninvasive testing. (*Level of Evidence: B*)
3. CABG is not recommended for patients with stable angina who have insignificant coronary stenosis (less than 50% diameter reduction). (*Level of Evidence: B*)

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**Unstable angina/non-ST-segment elevation MI (NSTEMI)**

**Class I**

1. CABG should be performed for patients with unstable angina/NSTEMI with significant left main coronary artery stenosis. (*Level of Evidence: A*)
2. CABG should be performed for patients with unstable angina/NSTEMI who have left main equivalent: significant (greater than or equal to 70%) stenosis of the proximal LAD and proximal left circumflex artery. (*Level of Evidence: A*)

## TABLE 27-1: American College of Cardiology/American Heart Association Guidelines for Coronary Artery Bypass Graft Surgery: Indications (*Continued*)

3. CABG is recommended for unstable angina/NSTEMI in patients in whom revascularization is not optimal or possible, and who have ongoing ischemia not responsive to maximal nonsurgical therapy. (*Level of Evidence: B*)

**Class IIa**

CABG is probably indicated for patients with unstable angina/NSTEMI who have proximal LAD stenosis with one- or two-vessel disease. ( *Level of Evidence: A*)

**Class IIb**

CABG may be considered in patients with unstable angina/NSTEMI who have one- or two-vessel disease not involving the proximal LAD when percutaneous revascularization is not optimal or possible. (If there is a large area of viable myocardium and high-risk criteria are met on noninvasive testing, this recommendation becomes class I.) (*Level of Evidence: B*)

---

**ST-segment elevation MI (STEMI)**

**Class I**

Emergency or urgent CABG in patients with STEMI should be undertaken in the following circumstances:

a. Failed angioplasty with persistent pain or hemodynamic instability in patients with coronary anatomy suitable for surgery. (*Level of Evidence: B*)
b. Persistent or recurrent ischemia refractory to medical therapy in patients who have coronary anatomy suitable for surgery, who have a significant area of myocardium at risk, and who are not candidates for PCI. (*Level of Evidence: B*)
c. At the time of surgical repair of postinfarction ventricular septal rupture or mitral valve insufficiency. (*Level of Evidence: B*)
d. Cardiogenic shock in patients less than 75 years old with ST-segment elevation or left bundle-branch block or posterior MI who develop shock within 36 h of MI and are suitable for revascularization that can be performed within 18 h of shock, unless further support is futile because of patient's wishes or contraindications/unsuitability for further invasive care (*Level of Evidence: A*)
e. Life-threatening ventricular arrhythmias in the presence of greater than or equal to 50% left main stenosis and/or three-vessel disease (*Level of Evidence: B*)

**Class IIa**

1. CABG may be performed as primary reperfusion in patients who have suitable anatomy and who are not candidates for or who have had failed fibrinolysis/PCI and who are in the early hours (6–12 h) of evolving STEMI. (*Level of Evidence: B*)
2. In patients who have had an STEMI or NSTEMI, CABG mortality is elevated for the first 3 to 7 days after infarction, and the benefit of revascularization must be balanced against this increased risk. Beyond 7 days after infarction, the criteria for revascularization described in previous sections are applicable. (*Level of Evidence: B*)

**Class III**

1. Emergency CABG should not be performed in patients with persistent angina and a small area of myocardium at risk who are hemodynamically stable. (*Level of Evidence: C*)
2. Emergency CABG should not be performed in patients with successful epicardial reperfusion but unsuccessful microvascular reperfusion. (*Level of Evidence: C*)

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**Poor LV function**

**Class I**

1. CABG should be performed in patients with poor LV function who have significant left main coronary artery stenosis. (*Level of Evidence: B*)
2. CABG should be performed in patients with poor LV function who have left main equivalent: significant (greater than or equal to 70%) stenosis of the proximal LAD and proximal left circumflex artery. (*Level of Evidence: B*)
3. CABG should be performed in patients with poor LV function who have proximal LAD stenosis with two- or three-vessel disease. (*Level of Evidence: B*)

**Class IIa**

CABG may be performed in patients with poor LV function with significant viable noncontracting, revascularizable myocardium and without any of the above anatomic patterns. (*Level of Evidence: B*)

**Class III**

CABG should not be performed in patients with poor LV function without evidence of intermittent ischemia and without evidence of significant revascularizable viable myocardium. (Level of Evidence: B)

(*Continued*)

## TABLE 27-1: American College of Cardiology/American Heart Association Guidelines for Coronary Artery Bypass Graft Surgery: Indications (*Continued*)

**Life-threatening ventricular arrhythmias**

**Class I**

1. CABG should be performed in patients with life-threatening ventricular arrhythmias caused by left main coronary artery stenosis. (*Level of Evidence: B*)
2. CABG should be performed in patients with life-threatening ventricular arrhythmias caused by three-vessel coronary disease. (*Level of Evidence: B*)

**Class IIa**

1. CABG is reasonable in bypassable one- or two-vessel disease causing life-threatening ventricular arrhythmias. (This becomes a Class I recommendation if the arrhythmia is resuscitated sudden cardiac death or sustained ventricular tachycardia.) (*Level of Evidence: B*)
2. CABG is reasonable in life-threatening ventricular arrhythmias caused by proximal LAD disease with one- or two-vessel disease. (This becomes a Class I recommendation if the arrhythmia is resuscitated sudden cardiac death or sustained ventricular tachycardia). (*Level of Evidence: B*)

**Class III**

CABG is not recommended in ventricular tachycardia with scar and no evidence of ischemia. (*Level of Evidence: B*)

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**CABG after failed PTCA**

**Class I**

1. CABG should be performed after failed PTCA in the presence of ongoing ischemia or threatened occlusion with significant myocardium at risk. (*Level of Evidence: B*)
2. CABG should be performed after failed PTCA for hemodynamic compromise. (*Level of Evidence: B*)

**Class IIa**

1. It is reasonable to perform CABG after failed PTCA for a foreign body in crucial anatomic position. (*Level of Evidence: C*)
2. CABG can be beneficial after failed PTCA for hemodynamic compromise in patients with impairment of the coagulation system and without previous sternotomy. (*Level of Evidence: C*)

**Class IIb**

CABG can be considered after failed PTCA for hemodynamic compromise in patients with impairment of the coagulation system and with previous sternotomy. (*Level of Evidence: C*)

**Class III**

1. CABG is not recommended after failed PTCA in the absence of ischemia. (*Level of Evidence: C*)
2. CABG is not recommended after failed PTCA with inability to revascularize due to target anatomy or no-reflow state. (*Level of Evidence: C*)

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**Patients with previous CABG**

**Class I**

1. Coronary bypass should be performed in patients with prior CABG for disabling angina despite optimal nonsurgical therapy. (If angina is not typical, then objective evidence of ischemia should be obtained.) (*Level of Evidence: B*)
2. Coronary bypass should be performed in patients with prior CABG without patent bypass grafts but with Class I indications for surgery for native-vessel CAD (significant left main coronary stenosis, left main equivalent, three-vessel disease). (*Level of Evidence: B*)

**Class IIa**

1. Coronary bypass is reasonable in patients with prior CABG and bypassable distal vessel(s) with a large area of threatened myocardium by noninvasive studies. (*Level of Evidence: B*)
2. Coronary bypass is reasonable in patients who have prior CABG if atherosclerotic vein grafts with stenoses greater than 50% supplying the LAD coronary artery or large areas of myocardium are present. (*Level of Evidence: B*)

who underwent DES placement versus 20 percent of patients who underwent CABG at 5 years of follow-up. The most powerful study to date is the SYNTAX trial, prospectively randomizing 1800 patients with left main coronary disease and/or three-vessel disease to either CABG or PCI with the paclitaxel drug eluting stent.[21] Most recently, the SYNTAX 3-year follow-up data revealed statistically significant differences favoring CABG in myocardial infarction, repeat revascularization, and MACCE. Stroke rates, which at one year significantly favored DES-treated patients, were no different between the two groups by three years.

There is a growing body of literature comparing PCI techniques with surgical revascularization. Although useful, the data must be interpreted critically in the context of the selection and exclusion criteria of patients within the trials. Recent technological advances have enlarged the pool of patients with single- or multivessel disease where percutaneous intervention is a reasonable alternative or even a preferred initial approach. However, patients and cardiologists must take into consideration the incidence of recurrent angina and need for repeat revascularization procedures. For patients who are not suitable for percutaneous intervention or when percutaneous intervention has failed, surgery should be strongly considered.

Patients presenting within 6 h of chest pain and an evolving myocardial infarction should be considered for early operation. However, owing to its rapidity in restoring vessel patency, percutaneous intervention has replaced surgery in most centers except in cases of associated mechanical complications (e.g., postinfarction ventricular septal defect, acute mitral insufficiency). An additional subgroup that may benefit from emergency CABG includes patients with acute proximal LAD occlusion and refractory/recurrent angina, since persistent pain reflects continued ischemia of viable myocardium. Emergency CABG is necessary when occlusive complications develop during percutaneous intervention. Most of these complications result from coronary artery dissections that begin as intimal defects caused by guidewire injury or balloon dilatation. In general, in performing emergency coronary artery bypass for these patients or those in cardiogenic shock, the initial goal is to quickly initiate cardiopulmonary bypass support, cardioplegic arrest, and cooling to reduce further myocardial damage. Not surprisingly, operative mortality and morbidity rates associated with emergency coronary bypass are greater than those occurring after elective or even urgent operations. This increased operative risk is often outweighed by the poorer outcome of nonsurgical treatment.

## PREOPERATIVE DATA

Comprehensive evaluation of the patient referred for CABG is obligatory. The cardiac surgeon's attention to detail leads to optimal risk assessment, preoperative preparation, operative planning, and postoperative care; these are all equally critical to the ultimate success of the operation. A complete history and physical is performed by the operative surgeon, with special attention to signs and symptoms of congestive heart failure, extracardiac organ dysfunction, concomitant valvular or peripheral vascular disease, previous conditions that may limit vascular conduit availability, and other comorbidities. Standard laboratory investigations include a complete blood count, electrolyte panel, renal and liver function tests, urinalysis, coagulation profile, and blood type and cross. Recent (e.g., within 1 month) anteroposterior and lateral plain chest radiography is reviewed, with particular attention to the cardiac silhouette, vascular calcifications, and pulmonic processes. At Johns Hopkins, when a plain chest film demonstrates aortic calcification, chest computed tomography is performed to further evaluate the ascending aorta for atherosclerotic plaques. A 12-lead ECG is obtained to establish conduction and ST-segmental baselines. Preoperative myocardial perfusion and viability studies—such as nuclear scintigraphy, stress tests, and magnetic resonance imaging—are reviewed to assist operative strategy and to assess the likelihood of surgical success. When a radial artery conduit is considered, Doppler evaluation of the nondominant hand is performed to assess ulnar artery collateralization. We routinely obtain bilateral carotid artery ultrasonography prior to coronary artery bypass, to screen for hemodynamically significant carotid stenosis.

Coronary angiograms are reviewed by all surgeons involved in the case. The coronary "road map" permits detailed examination of the coronary vessels for size, suitability, and priority for bypass. In addition, the relationships between the diseased vessels and regional wall motion abnormalities must be ascertained. Suggestions of aortic valvular insufficiency and mitral valvular regurgitation on left ventriculography should be further investigated with an echocardiogram.

Preoperative protection of the heart to minimize further myocardial damage is of utmost importance. Administration of β-blockers, nitrates, and calcium antagonists is continued to the operative date. Angiotensin converting enzyme (ACE) inhibitors are held for at least 24 h. For patients with unstable angina or intramural thrombus, intravenous heparin is continued up to 4 h prior to the operation. Placement of an intraaortic balloon pump is indicated when medical management fails to relieve angina or in cases of ischemic cardiogenic shock. Patients who come to surgery having received thrombolytics, such as alteplase, streptokinase, or reteplase, face a heightened risk of perioperative hemorrhage. More recently, the use of antiplatelet-aggregation drugs—such as abciximab (ReoPro), eptifibatide (Integrilin), tirofiban (Aggrastat), and clopidogrel (Plavix)—has become popular. If the patient's coronary syndrome is stable, it is advisable to discontinue these medications at an appropriate time (each has a different half-life) before the operation. At Johns Hopkins, we continue aspirin up to the date of surgery owing to recent data showing improved operative outcomes.

Although potential comorbid conditions affecting CABG outcomes are many, the patient's overall state of health and the potential for complete revascularization remain critically important. Incomplete revascularization due to severe

distal disease or inadequate conduit leads to higher mortality and a poor long-term prognosis. Seven adverse factors are known to influence survival: advanced age, ejection fraction, clinical status (e.g., shock, emergency surgery), female sex, diabetes, previous coronary artery bypass surgery, and congestive heart failure. Other comorbid conditions that should be addressed include previous stroke, history of significant bleeding, hypertension, angina class, concurrent infection (e.g., urinary tract, dental), chronic obstructive pulmonary disease (COPD), and hepatic and renal insufficiencies. Since 1989, the Society of Thoracic Surgeons has established a database of coronary and valvular cardiac operations performed in the United States. Surgeons can now obtain immediate risk stratification data for a given patient simply by entering clinical data online at http://www.sts.org.

## SURGICAL TECHNIQUES

The primary goal of coronary artery bypass surgery is to completely revascularize all significantly stenosed (i.e., 70 percent luminal narrowing or more) coronary arterial trunks and branches with a diameter of at least 1 mm. In patients with multivessel disease with a number of stenosed branches, sequential distal anastomoses may be required to conserve conduit length. The sequence of distal anastomoses usually entails grafting the most ischemic region first to allow early intraoperative administration of cardioplegia. However, pedicled grafts, such as the internal mammary artery, are usually anastomosed last to prevent inadvertent injury to these comparatively fragile tissues. Retrograde delivery of cardioplegia, in addition to antegrade delivery, is often prudent in the setting of significant left main coronary disease, severe three-vessel disease, and aortic insufficiency. When retrograde cardioplegia is used, it may be prudent to perform the right coronary artery distal anastomosis initially for early delivery of antegrade cardioplegia, since there is some evidence that retrograde delivery does not provide optimal right ventricular protection. We use a standard anastomotic sequence consisting of the right/inferior wall (i.e., right or posterior descending coronary) first, the lateral wall (i.e., circumflex marginal) second, and the anterior wall (e.g., LAD) last.

At Johns Hopkins, approximately 80 percent of primary coronary bypass operations are performed with cardiopulmonary bypass support under cardioplegic arrest. Over the last decade, much attention has been given to the application of minimally invasive approaches to coronary artery bypass surgery. Although robot-assisted cardiac surgery remains largely investigational and limited-access techniques on the arrested (e.g., Port-Access, Heartport) or beating heart [minimally invasive direct coronary artery bypass (MIDCAB)] have not been fully embraced, coronary revascularization on the beating heart without the use of cardiopulmonary bypass has gained popularity.

In some centers, off-pump coronary artery bypass (OPCAB) has become the primary method of surgical revascularization. Despite the theoretical benefit of avoiding the sequelae of cardiopulmonary bypass, convincing data demonstrating superior or equivalent graft patency rates as compared with conventional techniques, reduced morbidity and mortality, faster recovery, and lower health care costs are still lacking. In fact, a recent randomized study comparing on versus off-pump bypass procedures demonstrated a worse composite outcome (death from any cause, any revascularization, nonfatal myocardial infarct) at 1 year of follow-up in the OPCAB group.[22] OPCAB techniques are discussed in Chapter 28.

### Choice of Graft Conduits

Table 27-2 lists graft conduit options, their indications and contraindications, and patency rates. Multiple studies clearly demonstrate early and late survival benefits with the use of a pedicled internal mammary artery as a graft to the LAD; this pedicled graft should be used whenever possible. The right pedicled internal mammary artery graft can be used to bypass the right coronary artery or, when sufficiently long, can be tunneled through the transverse sinus to reach targets in the proximal left lateral wall. In patients less than 50 years of age, we routinely use bilateral mammary artery grafts unless the patient has diabetes, is obese, or suffers from severe COPD. There is some evidence to suggest that these conditions predispose to sternal wound complications if both mammary arteries are used. If the internal mammary artery is injured or has suboptimal flow, it can still be used as a free arterial graft.

The greater saphenous vein remains the primary source of free grafts. If it is absent or inadequate, the lesser saphenous vein is an option. When the saphenous vein is anticipated to be inadequate, bilateral radial artery grafts should be evaluated and prepared for harvesting as free grafts. Cephalic veins should be used only as a last resort. The inferior epigastric and gastroepiploic arteries can also be used as free grafts; however, limitations on length, inconsistent availability due to early branching and small caliber, and tedious dissection have made these infrequently used conduits. In our practice, we rarely use such unusual pedicled arterial conduits. Certainly such grafts should be avoided in emergency operations or with excessive cardiac enlargement. Alternative sources of graft conduits include cryopreserved human saphenous vein allografts, bovine internal mammary and sacral arteries, and various small-diameter synthetic (i.e., polyurethane, PTFE) conduits. All these alternative conduits exhibit unacceptably low patency rates or are not in active clinical use.

### Operative Technique

The median sternotomy is followed by internal mammary artery dissection (Fig. 27-1). We routinely inject the internal mammary artery with intraluminal papaverine and wrap the pedicled graft in a papaverine-soaked sponge. A full

**TABLE 27-2: Coronary Artery Bypass Conduit Indications, Contraindications, and Graft Failure Rate**

| | Indication | Contraindication | Failure rate |
|---|---|---|---|
| Left internal mammary artery | Whenever feasible | Emergency surgery | 3–8% at 1 year |
| | | Poor flow or injury | 4–12% at 5 years |
| | | Subclavian artery stenosis/occlusion | 7–12% at 10 years |
| Right internal mammary artery | Young patient | Diabetes (relative) | |
| Free internal mammary artery graft | When internal mammary artery cannot be used as pedicled graft | Atherosclerotic or dissection | 8–25% intermediate term |
| Radial artery | Arterial conduit | Positive Allen test | 15% at 3 months further 7% during next 6 months |
| | | Incomplete palmer arch | |
| | | Prior carpal tunnel operation | |
| | | Prior radial arterial cannulation (relative) | |
| Gastroepiploic artery | Additional arterial conduit | Prior gastric resection | 4% at 2 months 8% between 2 and 5 years |
| | | Atherosclerosis of celiac axis | |
| | | Emergency surgery | |
| | | Large heart | |
| | | Severe LV dysfunction | |
| Inferior epigastric artery | Lack of other conduits | Paramedian abdominal incision | 21% at 5 years |
| | Prior use of internal | Atherosclerosis | |
| | Mammary artery | Previous groin incision (relative) | |
| Greater saphenous vein | Best venous conduit | Too small (<2 mm) | 10–15% in first month |
| | | | 2–3% per year between 1 and 5 years |
| | | | 5% per year after 5 years |
| | | | 50% in 10 years + 25% |
| | | | With stenosis |

therapeutic dose of heparin (300 U/kg) is given at this time to achieve an activated clotting time (ACT) of 480 s (550s if aprotinin is used). After confirming that the internal mammary artery and saphenous vein grafts are satisfactory, a standard pericardial well is created. At this time, the ascending aorta is palpated to detect potential plaques and select a cannulation site. Obvious calcified plaques are avoided. In some centers, epiaortic echocardiography is used to survey the ascending aorta prior to cannulation. The aorta and pulmonary artery reflection is divided, obtaining adequate space in the aortopulmonary window to permit aortic cross clamping. We use two 2-0 braided purse-string sutures placed in the adventitial layer for aortic cannulation; the preferred position is just inferior to the innominate artery takeoff along the lesser curvature of the aorta. For most adults, a 20F Soft-Flo aortic cannula (Sarns, Inc., Ann Arbor, MI) provides maximal flow rates of up to 5800 mL/min. Once the position of the aortic cannula tip is confirmed, the arterial limb of the cardiopulmonary bypass circuit is connected. For uncomplicated, isolated coronary artery bypass, we prefer using a single dual-stage cannula for venous drainage. Usually a 32/34F cannula is adequate, especially if vacuum assistance is used. Larger patients may require larger cannulas. The venous cannula is placed through a purse-string stitch consisting of 2-0 braided suture placed in the right atrial appendage. For primary elective coronary artery bypass, cardiotomy suction is no longer used to reduce the risk of particulate emboli returning to the bypass circuit. Shed mediastinal blood is returned to the patient via cell-saver recovery. A 4-0 polypropylene horizontal mattress stitch is placed in the midascending aorta to secure the antegrade cardioplegia cannula.

Once a satisfactory ACT is confirmed and the cardiopulmonary bypass lines have been checked for kinks or clamps, cardiopulmonary bypass is initiated and conducted with nonpulsatile flow of 1.8 to 2.2 L/min/$m^2$ with a target mean arterial peripheral pressure of 50 mm Hg, or higher if the patient has significant peripheral vascular disease. The pulmonary artery is routinely vented. The systemic temperature is allowed to drift initially and then is lowered to 34°C or lower when a prolonged bypass period is expected. The cardioplegia line is flushed free of air. We primarily employ antegrade blood cardioplegia with or without retrograde supplementation. At Johns Hopkins, a 2:1 mixture of blood to high-potassium crystalloid solution (50 mEq sodium bicarbonate and 60 mEq

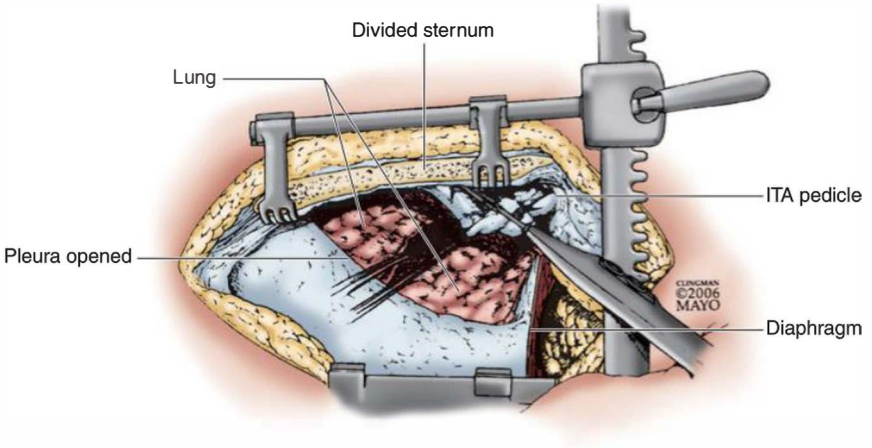



**FIGURE 27-1** Harvesting of left internal thoracic artery. An asymmetrical retractor is used to elevate the left hemisternum. The parietal pleura and endothoracic fascia medial and lateral to the internal thoracic artery and accompanying veins are incised with the electrocautery and then, using a combination of blunt and electrocautery dissection, the pedicle of the internal thoracic artery is separated from the chest wall. Metal clips are used to secure the larger branches. The pedicle can be harvested from the level of the subclavian vein down to the bifurcation of the superior epigastric and musculophrenic arteries. After systemic heparinization, the pedicle is divided distally and flow is assessed. (Reproduced with permission from Mayo Foundation for Medical Education and Research. All rights reserved.)

potassium) is administered approximately every 20 min. If retrograde cardioplegia is used, the coronary sinus pressure is monitored and maintained at 35 mm Hg during infusion.

To initiate arrest, the distal ascending aorta is cross-clamped proximal to the arterial cannula and 800 to 1000 mL of cold blood cardioplegia is administered in an antegrade manner. The surgeon confirms an adequate aortic root pressure and the absence of left ventricular distention. Additional myocardial cooling is provided by continuous topical irrigation with cold saline instilled into the pericardial well; the irrigant is cleared by a discard suction device. Once cardiac arrest is achieved, the heart is elevated to inspect the coronary anatomy and distal graft sites.

Silastic loops are placed proximal and distal to the intended site of the coronary arteriotomy to facilitate anastomosis. The arteriotomy, made at an axial plane to the course of the target artery, is constructed in a standard end-to-side manner with a running 7-0 Prolene suture (Fig. 27-2). Many surgeons elect to perform sequential anastomoses to perfuse two or more coronary arteries with a graft. This entails the construction of one or more side-to-side anastomoses (Fig. 27-3). Besides conserving graft conduit length, this technique augments graft outflow (i.e., lower resistance to flow), which many believe tends to provide greater graft patency. After each free graft distal anastomosis is constructed, the graft is flushed with approximately 100 mL of blood cardioplegia. Bleeding sites on the vein graft and at the anastomosis can then be easily identified and repaired. After all of the distal free graft anastomoses are completed, the mammary artery is dissected free from its pedicle and the tip prepared for anastomosis. Adequate flow in the internal mammary artery is confirmed and the distal anastomosis, usually to the LAD, is constructed in an end-to-side fashion.

Free graft proximal anastomoses are generally performed with the cross-clamp in place. Some surgeons prefer to use a partial occluding clamp to permit coronary perfusion during performance of the proximal anastomoses; others prefer to minimize manipulation of the aorta. Small 4.0-mm aortotomies are created with an aortic punch. Proximal anastomoses are generally constructed with 5-0 or 6-0 Prolene in an end-to-side fashion (Fig. 27-4). Prior to securing the final proximal anastomosis, the pulmonary vent is turned off and the heart is filled with blood. Air is then evacuated from the ascending aorta through the last unsecured proximal suture line, which is subsequently tied. The aortic cross clamp is then removed. The pulmonary arterial vent is removed and its site oversewn. Once the surgeon elects to wean from cardiopulmonary bypass, the anesthesiologist is asked to resume ventilation. Cardiopulmonary bypass is then gradually weaned to off, the heart is decannulated, and heparin reversal with protamine is initiated. Appropriate mediastinal and pleural drains are placed and the chest is closed.

## SPECIAL CONSIDERATIONS

### The Atherosclerotic Aorta

Embolization of atherosclerotic debris from a severely atherosclerotic aorta is generally considered the primary cause

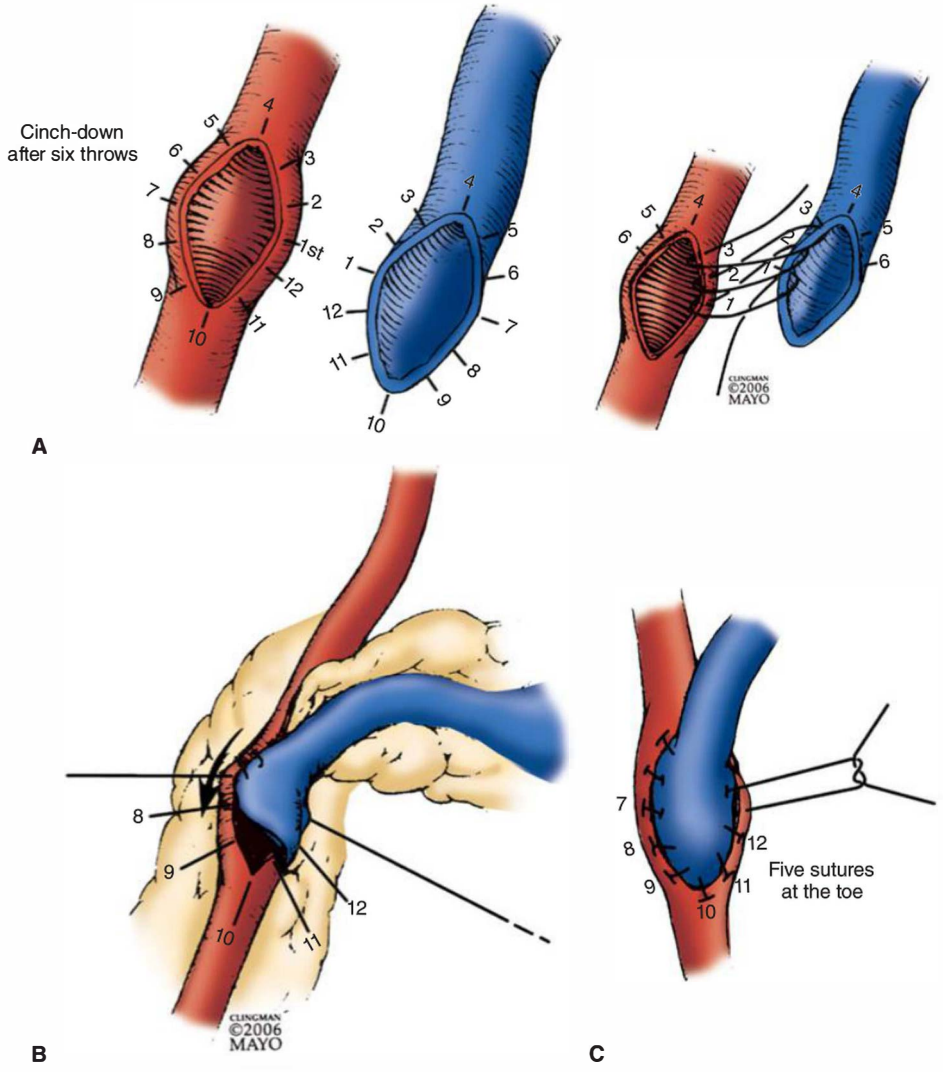



**FIGURE 27-2** Distal anastomosis. **A.** A fine polypropylene suture is passed through the conduit and coronary artery in a running fashion toward and around the anastomotic heel. **B.** After several throws, the conduit is gently parachuted down to the coronary artery. **C.** A suture is continued toward and around the anastomotic toe until the other end of the suture is reached. (Reproduced with permission from Mayo Foundation for Medical Education and Research. All rights reserved.)

of perioperative stroke in CABG patients. Aortic plaque can be assessed initially with manual palpation; however, this method can easily miss noncalcified atheromas. The most sensitive modality whereby aortic atherosclerosis can be assessed is epiaortic ultrasonographic scanning.

In some cases of patchy ascending aortic disease, "safe" sites for application of the cross-clamp and construction of proximal anastomoses can be identified. In these cases, side-biting partial aortic clamps should be avoided. When extensive aortic calcification is identified (e.g., "porcelain" aorta), OPCAB is a reasonable alternative to avoid cross-clamping the aorta. Proximal anastomoses can be constructed in this setting with one of several commercial anastomotic device systems. Other alternatives include conducting the surgery under fibrillatory arrest, replacement of the ascending aorta with a Dacron graft, or basing free grafts on the internal mammary artery pedicle.

## Failure to Wean from Cardiopulmonary Bypass

When the patient cannot be successfully weaned from cardiopulmonary bypass, an assessment of the reasons for failure must be efficiently conducted. A review of existing biventricular contractility, adequacy of inotropic/pharmacologic

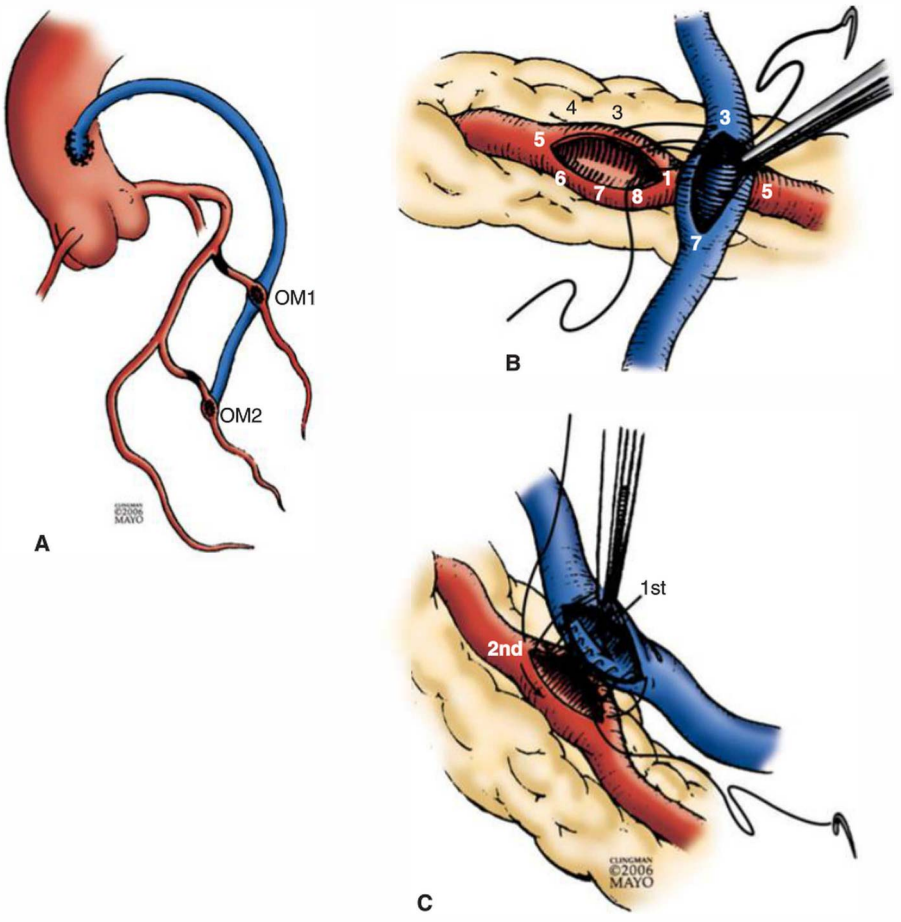



**FIGURE 27-3** Sequential distal anastomosis. **A.** Determination of the appropriate geometric alignment of the conduit and coronary artery. **B.** Coronary arteriotomy and conduit venotomy or arteriotomy are created. **C.** In a manner similar to that described for distal anastomosis, a polypropylene suture is used in continuous fashion beginning near t he heel. (Reproduced with permission from Mayo Foundation for Medical Education and Research. All rights reserved.)

support, optimal cardiac function (e.g., adequate volume and heart rate), metabolic conditions (e.g., acidosis, hyperkalemia), and bypass graft patency must be carefully performed.

Manual palpation of bypass grafts can be misleading, as an occluded graft can display accentuated pulsatility. Doppler ultrasonography with a flow probe can provide an accurate assessment of the patency of either venous or arterial graft conduits. Poor flow in a newly constructed bypass graft is almost always due to technical error; such grafts should be revised prior to further attempts at weaning from cardiopulmonary bypass. It is often prudent to re-review the preoperative coronary angiogram to determine whether nongrafted territories should be addressed. Transesophageal echocardiography is an important modality to (1) identify new or old regional wall abnormalities that may be relieved by additional revascularization and (2) recognize any intracardiac factor, such as valvular dysfunction or previously undetected shunting that may be contributing to the failure to wean.

If, despite optimization of all correctable parameters, separation from cardiopulmonary bypass remains impossible, mechanical assistance is indicated. Intraaortic balloon pump counterpulsation is usually the initial option to improve coronary perfusion and reduce ventricular afterload. Its use and contraindications are discussed elsewhere in this book. Further inability to wean will require the use of formal ventricular assist devices if the patient meets the criteria for their implantation.

## POSTOPERATIVE RECOVERY

Early postoperative management of CABG patients does not differ significantly from that of other cardiac surgical patients and is not covered in detail here. In general, patients who undergo primary coronary artery bypass are quickly weaned off mechanical ventilatory support and extubated.

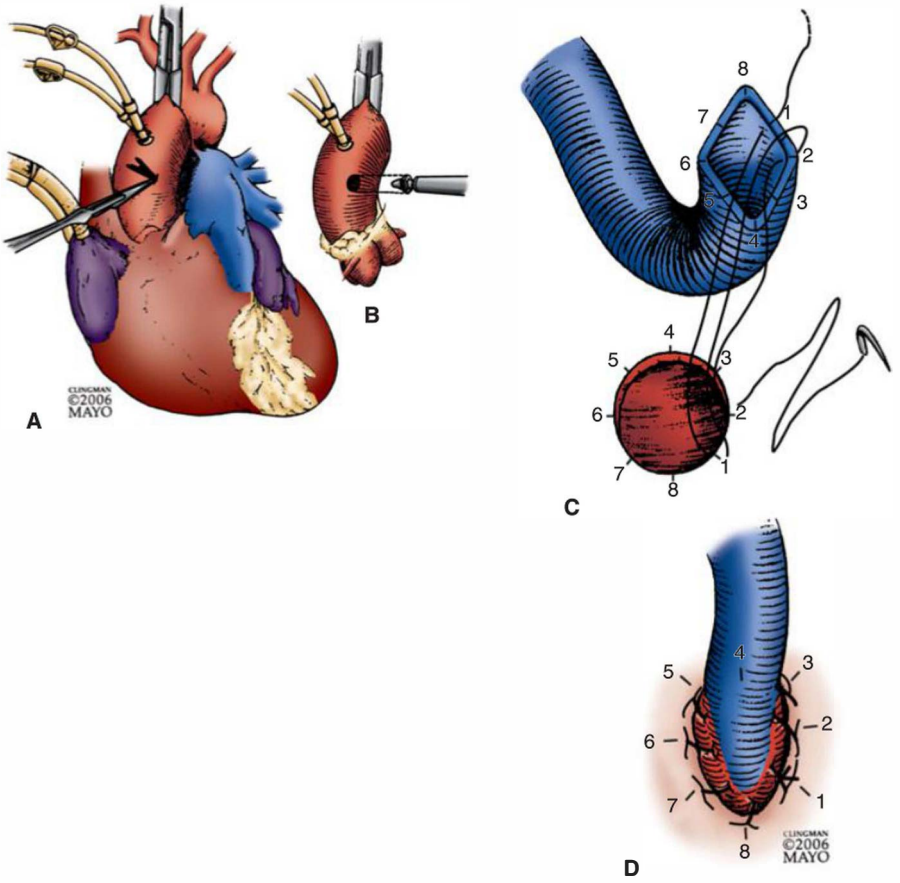



**FIGURE 27-4** Proximal anastomosis. **A.** The technique of single cross-clamping is demonstrated. An aortotomy is created with a knife and punch. Appropriate conduit length and orientation are established and a fine polypropylene suture is used in a running fashion toward and around the anastomotic heel. **B.** The conduit is then carefully parachuted down onto the aorta. **C.** The suture is continued toward and around the anastomotic toe. **D.** The completed anastomoses. (Reproduced with permission from Mayo Foundation for Medical Education and Research. All rights reserved.)

Parenteral inotropes and intraaortic balloon pumps are weaned as appropriate. We do not routinely use pulmonary artery catheterization in this patient population; however, when indicated, it can assist in the management of hemodynamic performance in the early postoperative period. A 12-lead ECG is obtained early after the patient arrives in the intensive care unit and compared with a preoperative ECG. Serial ECGs are obtained to detect new ischemia. We do not routinely obtain postoperative cardiac enzyme markers. On the first postoperative day, mediastinal and pleural chest tubes are removed if drainage is less than 30 mL/h for 4 consecutive hours. β-Blockers and aspirin are administered early if there are no hemodynamic or coagulation issues. We now routinely load our patients orally with amiodarone (400 mg/day for 5 days, followed by 200 mg/day) as prophylaxis for atrial dysrhythmias. Some surgeons elect to administer clopidogrel along with aspirin in the early postoperative period to address growing evidence for aspirin resistance in some patients. Since several trials have demonstrated that an aggressive lipid-lowering strategy confers beneficial effects on graft patency, we now routinely administer lovastatin or an equivalent drug postoperatively.

Once deemed stable, patients are transferred from the intensive care unit to a monitored step-down unit and are actively ambulated with the assistance of physical therapists. If pacing wires have been placed and there are no concerning arrhythmias, they are removed by the second postoperative day. A coordinated program of physical therapy and dietary management should be initiated as soon as the patient leaves the hospital. Inpatient or outpatient rehabilitation and physical therapy are arranged as needed. Patients who smoke must give up tobacco; this may require pharmacologic nicotine replacement. Preoperative emphasis on smoking cessation can be invaluable. Other modifiable risk factors for coronary atherosclerosis, such as hypertension and hyperlipidemia, should be monitored and controlled in a comprehensive program to promote graft patency.

## Acute Postoperative Myocardial Ischemia/Infarction

Early postoperative myocardial ischemia and/or infarction, especially when associated with hemodynamic disturbances, can exert major adverse effects on operative outcomes. A postoperative myocardial infarction, defined by new Q waves on the postoperative ECG, occurs in 4 to 5 percent of patients. A new Q-wave myocardial infarction is usually attributed to poor distal perfusion, but it can be also be due to incomplete revascularization, technical graft failure, inadequate myocardial preservation, or inadequate resuscitation in the early postoperative period. Cardiomegaly, prolonged cardiopulmonary bypass, reoperative coronary artery bypass surgery, and bypass grafting combined with other cardiac operations are known risk factors for postoperative myocardial infarction. Other factors identified from the Coronary Artery Surgery Study (CASS) trial predictive of postoperative myocardial infarction include female gender, severe preoperative angina pectoris, severe left main coronary stenosis, and three-vessel disease.[23]

Accurate diagnosis of a myocardial infarction after cardiac surgery requires an integrated approach that combines laboratory and clinical findings. Although new, persistent Q-waves on ECG are suggestive of postoperative myocardial infarction, nonspecific ST–T-segment abnormalities on ECG and typical postoperative elevations of biochemical markers (e.g., creatinine kinase, troponin) are frequently not definitive. Nevertheless, when suspicious ECG changes are associated with hemodynamic and/or rhythm disturbances, postoperative myocardial ischemia should be ruled out. Patients with ST–T-segment elevations and a low cardiac index should prompt consideration of intraaortic balloon pump support. Bedside transthoracic or, when necessary, transesophageal echocardiography can provide valuable supportive data if regional wall motion abnormalities are seen, especially if they correlate with ECG findings. When an integrated review of these diagnostic modalities and clinical indications are highly suggestive of an acute postoperative myocardial ischemia/infarction, immediate coronary angiography is indicated. Subsequent percutaneous intervention or operative rescue is determined based on the clinical situation.

# OUTCOMES

Coronary artery bypass surgery is the most scrutinized operation historically and currently. Public distribution of revascularization outcomes is a modern reality for the cardiac surgeon. There is a tremendous amount of literature analyzing, comparing, and modifying CABG outcomes. Below, we focus upon the nature of early post-CABG mortality, important postoperative complications, and positive outcome variables.

## Perioperative Mortality

Early in-hospital mortality from primary coronary artery bypass surgery has seen a steady decline from the 1970s into the 1990s. Recently, however, the patient population referred for coronary artery bypass has become increasingly complex, hence the decline has plateaued in recent years. Older patients, more advanced and diffuse coronary artery disease, worsening left ventricular function, failure of multiple previous percutaneous manipulations, more serious comorbidities, and a greater frequency of reoperation have contributed to an increase in perioperative risk. Therefore, only risk-adjusted outcome data can be truly informative. Currently, the overall operative mortality rate for CABG is about 3 percent; elective primary coronary artery bypass carries a mortality rate of 1.2 percent, according to the database of the Society of Thoracic Surgeons.

## Perioperative Morbidity

As a consequence of CABG performed on higher-risk patients, most cardiac surgeons have witnessed an increase in the rate of postoperative complications. Perioperative myocardial infarction has been covered previously; this section reports other common operative morbidities.

### HEMORRHAGE

Coagulopathy, platelet dysfunction/depletion, and the release of proinflammatory factors are recognized consequences of cardiopulmonary bypass. Even with OPCAB and the use of antifibrinolytics such as aminocaproic acid (Amicar), significant bleeding still occurs. The rate of reexploration for bleeding following conventional coronary artery bypass ranges from 2 to 6 percent. Risks for bleeding include older age, preoperative aspirin and other antiplatelet agents, reoperation, nonelective surgery, prolonged cardiopulmonary bypass time, and five or more bypass grafts.[24]

### MEDIASTINITIS

Deep sternal wound infections occur in 1 to 4 percent of primary coronary artery bypass patients. This complication clearly increases mortality and may bring long-lasting morbidity to the patient. Obesity, the use of bilateral internal mammary grafts, diabetes, prolonged operation, and prior coronary artery bypass are all risk factors for mediastinitis. Appropriate and timely administration of perioperative antibiotics, meticulous skin preparation, and attention to sterile technique can help minimize this troublesome complication.

### RESPIRATORY INSUFFICIENCY

Prolonged ventilator dependence (e.g., more than 1 day) occurs in approximately 6 percent of CABG patients. Many factors contribute to postoperative respiratory failure, but

preexisting pulmonary disease is the most important predictor. Other factors that are associated with prolonged ventilation include: female gender, BMI less than 20 kg/m$^2$, mitral valve disease, prior CABG, and prior cerebrovascular accident.[25] Coronary artery bypass patients with severe COPD have significantly higher mortality rates (19 percent) than those with mild to moderate or no COPD.

### NEUROLOGIC COMPLICATIONS

Adverse neurologic outcome following coronary artery bypass surgery is the subject of intense investigation. It is a dreaded complication that can manifest in numerous ways. Nearly three-quarters of coronary artery bypass patients experience some degree of neuropsychologic derangement, which tends to be transient. However, persistent or permanent significant neurologic deficits are important causes of postoperative mortality and morbidity. In general, a *type I deficit* is associated with a major focal deficit and/or stupor or coma; a *type II deficit* is characterized by a measurable deterioration of intellectual function and memory. Known factors contributing to type I deficits include older age, ascending aortic atherosclerosis, history of stroke, use of intraaortic balloon pump, diabetes, hypertension, and unstable angina. In a prospective study of just over 5000 patients at our institution, delirium was shown to be an independent risk factor for long-term mortality after CABG.[26]

### ATRIAL FIBRILLATION

Up to 40 percent of CABG patients will experience at least one episode of atrial fibrillation. It is the most frequent post operative rhythm disturbance and usually occurs on the second or third postoperative day. Although usually benign and self-terminating, atrial fibrillation is associated with prolonged hospitalization, hemodynamic instability, and thromboembolism. The stroke risk in patients experiencing postoperative atrial fibrillation is increased threefold. The exact mechanism behind this dysrhythmia is likely multifactorial, including increased endogenous catecholamine levels, atrial ischemia, and atrial reentrant pathways. The recent routine use of β-blockade has significantly reduced its incidence. At Johns Hopkins, we routinely use amiodarone to prevent postoperative atrial fibrillation.

### RENAL DYSFUNCTION

Up to 8 percent of CABG patients develop postoperative renal dysfunction. Nearly 18 percent of these patients required hemodialysis, which significantly increases their mortality rate. Predictors of renal dysfunction include advanced age, baseline renal disease, diabetes, poor cardiac function, previous coronary artery bypass surgery, peripheral vascular disease, and use of intraaortic balloon pump counterpulsation. Coronary angiography is necessary for preoperative planning. However, dye exposure leads to an increase in postoperative renal failure. Angiography performed within 24 h prior to operation increases the rate of postoperative renal failure from 8.8 percent to 31 percent.[27] Although patient convenience is an important goal, elective cardiac catheterization should be performed more than 24 h prior to surgery.

## Angina Relief

Coronary artery bypass surgery is highly effective in relieving anginal symptoms and improving quality of life. Randomized trials consistently show that surgical revascularization confers more durable symptomatic relief than medical or percutaneous therapies. Approximately 80 percent of coronary artery bypass patients are angina-free at 5 years and 63 percent at 10 years.[28] The return of angina has an early phase that peaks at about 3 months postoperatively and a late phase that peaks at 3 years. The early phase is likely due to incomplete revascularization and graft failure, while late phase results from progression of native coronary artery disease and late stenosis/occlusion of bypass grafts. Recurrent angina, whether early or late, indicates repeat coronary angiography to dictate whether percutaneous intervention or reoperation is necessary. Predictors of angina recurrence include female gender obesity, hypertension, incomplete revascularization, and absence of the internal mammary artery graft.

## Return to Work

The ability to return to employment is another important endpoint in CABG outcome analyses. There is no universal agreement on whether coronary artery bypass surgery confers an advantage in obtaining or maintaining gainful employment. Clearly, those patients employed prior to surgery are most likely to return to work after surgery. Also, CABG patients in the middle of their professional productive years are more inclined to continue working. In general, among patients employed shortly before CABG, 80 percent are back to work a year later. Among patients with unfavorable factors—such as older age, return of angina, and preoperative unemployment or disability—less than 20 percent returned to work.[29]

## Long-Term Survival

After an early nadir within the first 6 postoperative months, mortality rates after CABG increase steadily after 1 year. The increase in the hazard ratio at 15 years is twice that at 5 years. Late death is mostly due to noncardiac causes; however, progression of native coronary disease and graft atherosclerosis continues to plague these patients. Updated data obtained from the CASS registry shows that 97 percent of CABG patients are alive at 1 year, 90 to 92 percent at 5 years, 74 to 81 percent at 10 years, and 56 to 66 percent at 15 years.[30]

## SUMMARY

Primary coronary artery bypass surgery remains the cornerstone of treatment for ischemic heart disease. For patients with advanced multivessel coronary artery disease or those with left ventricular functional impairment, surgical revascularization still provides greater symptomatic relief and superior survival rates than medical or percutaneous interventional therapies. Although minimally invasive techniques and OPCAB have generated much investigation and controversy, over three-quarters of all CABGs performed in the United States are performed with conventional cardiopulmonary bypass support. Employment of an all-arterial versus saphenous vein-supplemented conduit strategy is still an active arena of debate.

Despite a steady increase in the proportion of older or "high-risk" patients being referred for surgery, major perioperative mortality and morbidity continues to be low, and long-term outcomes are excellent. Years of surgical innovation and experience have set the standard against which future advances in PCI, molecular therapeutics, and novel surgical approaches will be compared.

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## PRIMARY CORONARY ARTERY BYPASS SURGERY BOARD REVIEW QUESTIONS (CHAPTER 27)

1. Which of the following is true regarding coronary artery anatomy?
   A. Ninety percent of people have a right dominant coronary artery system.
   B. The coronary ostia are rarely located outside their respective sinuses.
   C. The most frequent coronary artery anomaly is origin from the noncoronary sinus.
   D. An aberrant circumflex artery is typically large and supplies the majority of the inferior wall.
   E. Congenital aortic stenosis has a higher incidence of left coronary dominance.

2. Which of the following is true regarding morphology of coronary artery disease?
   A. Most acute myocardial infarction results from plaque hemorrhage, swelling, and subsequent coronary occlusion.
   B. Complete occlusion of one coronary is not commonly associated with significant lesions in other coronary arteries.
   C. The LAD and RCA systems are more commonly involved than the circumflex system.
   D. Transmural infarctions are characterized by complete absence of viable muscle cells in the infarct area.
   E. Acute infarction usually occurs in a chronic, severely narrowed vessel.

3. Which of the following is true regarding results of coronary artery bypass?
   A. Average 10-year survival is about 75 percent.
   B. The third rising phase of hazard of death is not affected by IMA grafting.
   C. Cardiopulmonary bypass time is not a procedural risk factor for death.
   D. Risk of death is strongly increased by increasing number of stenosed vessels.
   E. Coronary artery bypass should ideally be performed within one week of acute myocardial infarction to reduce risk.

4. Which of the following statements is true regarding indications for coronary artery bypass?
   A. 50 percent left main stenosis is equally well treated with PTCA or CAB.
   B. Patients with three-vessel disease, good LV function, and mild ischemia should have urgent operation.
   C. CAB is indicated in two-vessel disease and depressed LV function.
   D. Depression of LV function below 20 percent is an absolute indication for CAB.
   E. Acute hemodynamic instability after acute MI is a contraindication to emergent CAB.

5. Which is true regarding outcomes after CAB?
   A. Up to 75 percent of patients have evidence of subtle neurobehavioral deficits.
   B. Gross neurologic deficit occurs in about 20 percent of patients over age 75.
   C. Functional capacity is not improved after operation.
   D. Less than 50 percent of patients have improvement in regional perfusion defects.
   E. Only hypokinetic areas can be expected to have improved systolic function.

## ANSWERS

1. **Answer: E.** Congenital aortic stenosis is associated with nearly a two-fold incidence of left coronary dominance. About 75 percent of people have a right dominant system. Up to 30 percent of right coronary ostia and up to 10 percent of left coronary ostia are located in the tubular portion of the aorta, above the sinus. The most frequent coronary artery anomaly is origin of the circumflex artery from the right coronary sinus. An aberrant circumflex artery is usually diminutive, underdeveloped, and supplies only a small area of the lateral wall.
2. **Answer: C.** Coronary artery disease more commonly involves the LAD and RCA. Most acute infarctions results from plaque rupture and thrombotic occlusion, not swelling. Ninety-five percent of patients with a completely occluded coronary artery will have a significant stenosis of at least one other coronary artery. Most transmural infarctions will have scattered islands of viable myocardial cells and are not completely acellular. Chronically stenotic arteries often have collateral circulation that provides some protection in acute occlusion.
3. **Answer: A.** Ten-year survival after coronary artery bypass is about 75 percent. The rising third phase of hazard is favorably affected by IMA grafting. Increased CPB time is a known risk factor for death after CAB. The number of stenosed vessels is only a weak risk factor. CAB performed within 8 days of acute myocardial infarction is associated with increased risk.
4. **Answer: C.** CAB is indicated for two-vessel disease and depressed LV function. Left main stenosis of 50 percent or greater is best treated with CAB. Medical management is appropriate for patients with three-vessel disease, preserved LV function, and only mild symptomatology. Risk of CAB may outweigh benefits in patients with severely depressed LV function. Emergent CAB can salvage over 50 percent of patients with acute hemodynamic instability after acute MI.
5. **Answer: A.** Up to 75 percent of patients will have subtle neurobehavioral deficits, but only 10 to 30 percent will persist at 3 months. Gross neurologic deficit occurs in about 8 percent of patients over age 75. Both maximal and function capacity are improved after operation. Over 2/3 of patients will have improvement in regional perfusion defects. Hypokinetic, akinetic, and dyskinetic areas can all show improved systolic function after surgery.

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28

# Off-Pump Coronary Artery Bypass

*Eric A. Peck*
*Paul Sergeant*

**KEY CONCEPTS**

- Team approach
  - Although all cardiac operations require a multidisciplinary approach, this is especially true for off-pump coronary artery bypass grafting (CABG). Close and clear communication with the anesthesiologist is critical for the safe performance of the procedure. Similarly, the nursing staff should be included in the dialogue so that it can anticipate each step in the operation and prepare instruments, shunts, and sutures as necessary and in a timely fashion.
- Minimization of risk
  - Off-pump CABG has the potential to reduce morbidity and mortality significantly. However, if done improperly, it can lead to higher complication rates. This is best avoided by minimizing potential intraoperative risk at every possible step.
- Reengineering
  - To achieve optimal results with this technique, it must be realized that this procedure is not just a CABG performed without the assistance of cardiopulmonary bypass. Instead, it requires a complete reengineering of the operative technique and physiologic concepts, including optimizing oxygen supply and demand and maintaining hemodynamic stability before, during, and after cardiac manipulation.

## INTRODUCTION

This will focus on the surgical technique that we feel provides the most effective and safe method of off-pump coronary revascularization.

Off-pump coronary artery bypass (OPCAB) has been practiced to some degree for many years, but it has regained popularity only recently with the development of devices that allow for superb exposure and stabilization of the anastomotic area. This technology continues to develop and improve over time. With the spectrum of patients presenting with coronary disease becoming more complex and higher risk, surgeons have been looking for surgical options that may reduce complications. OPCAB has this potential because it avoids cardiopulmonary bypass (CPB) and the associated morbidity.

OPCAB is not simply the standard coronary bypass operation performed without the assistance of CPB. Rather, it is a concept whose primary goal should be the reduction of morbidity and mortality. The technical result should be identical to that for a standard coronary artery bypass graft (CABG) operation: the same number, location, and quality of anastomoses. Further, OPCAB must be a reproducible technique, allowing it to be taught to other surgeons and incorporated into the training of cardiothoracic surgical residents. This aspect is something that has been studied in a scientific fashion at Gasthuisberg Hospital in Belgium. There are now objective data to support this technique, which can be safely taught to residents and can also be used to retrain established surgeons.[1] Ideally OPCAB should be applicable to the entire spectrum of patients. In Leuven, a practical algorithm is used to determine whether a particular patient has a bypass performed with or without CPB (Fig. 28-1). Obviously, for any patient in extremis, receiving cardiac compressions, or with malignant arrhythmias, emergent institution of CPB is lifesaving and necessary. In this patient subset, the authors perform CABG on CPB, but with a beating heart to minimize further ischemia. In more stable patients, the next branch in the decision tree involves whether the patient has had an acute infarct (within 3 days of surgery). Regardless of other risk factors or comorbidities (e.g., complexity of coronary lesions, cardiomegaly,

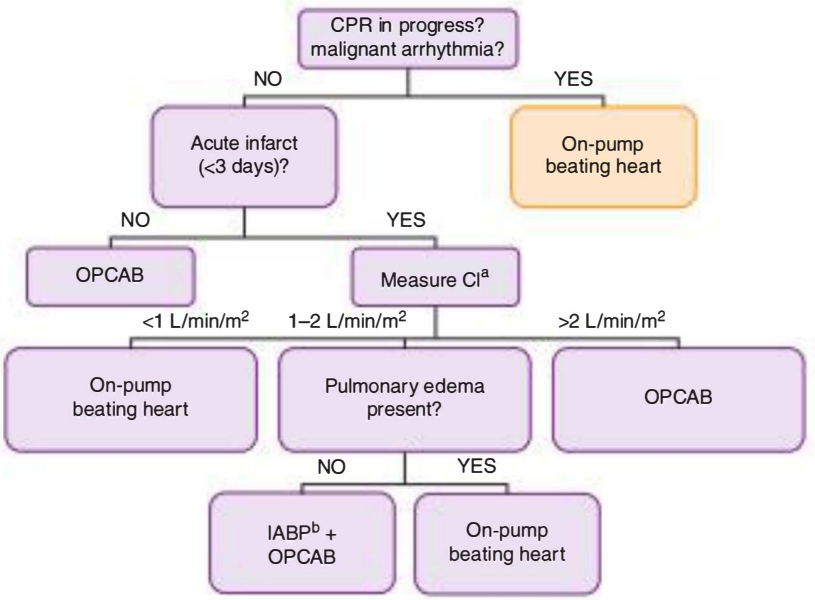



**FIGURE 28-1** Algorithm used to determine method for performing off-pump and on-pump coronary artery bypass grafting. (With permission from Peck EA, Sergeant PL. Leuven, Belgium.)

redo surgery, ejection fraction), if the infarct is more than 3 days old, the procedure is performed off-pump. For an acute infarct, a pulmonary artery (PA) catheter is placed and the cardiac index (CI) is measured. If the CI is less than 1 L/min/m$^2$, the patient is placed on CPB and the revascularization is completed with the heart beating. For patients with a CI greater than 2 L/min/m$^2$, procedures are performed off-pump. In patients with a CI between 1 and 2 L/min/m$^2$, a determination is made as to the presence or absence of pulmonary edema. The authors believe that pulmonary vascular congestion is an indication of severe left ventricular dysfunction and indicates a patient who probably will not tolerate cardiac manipulation and may need assistance with oxygenation. These patients undergo CABG with CPB, but with the heart beating.

A less evident component of a successful OPCAB program is the ability to perform these procedures without undue stress on the operating team: surgeons, anesthesiologists, and nurses. Many teams feel averse to performing OPCAB because of the level of anxiety that results from conducting this technique under suboptimal conditions. Hemodynamic instability, ischemia, unpredictability, and perhaps an open confrontation between the anesthetic and surgical teams all contribute to this. The structured environment and organized, stepwise technique developed by one of the authors (Dr. Sergeant) has created an atmosphere of collegiality and open communication, eliminating these stressful triggers and leading to a pleasant operating environment.

This approach involves a number of factors geared toward minimizing risk and enhancing the safety of the procedure. The key to this is the optimization of intraoperative patient hemodynamics (i.e., heart rate/rhythm, blood pressure, cardiac filling pressures, electrolytes, and body temperature) before cardiac manipulation. This provides a stable platform that allows the surgeon to enucleate the heart from the pericardium safely during the anastomotic period. Further, it optimizes the myocardium to tolerate any transient ischemia that is produced. Without proper anesthetic conditioning, the entire concept of OPCAB can be unsafe and the operation should not be performed. Each step in the authors' technique is designed to eliminate or reduce the risk associated with off-pump revascularization. Not all steps are essential for every coronary anastomosis in every patient. However, it is challenging to predict which circumstances will produce instability for any specific patient and/or anastomosis, and it is for this reason that the authors use the safeguards in every patient and for every anastomosis. Without such stringent controls, a certain percentage of patients will require urgent/emergent conversion to on-pump CABG, which clearly has been shown to result in significant morbidity and mortality.[1-3]

Surgeons also must be able to perform anastomoses in smaller spaces and on vessels that may be at unfamiliar angles. To maintain hemodynamic stability, the heart must be manipulated so that mitral insufficiency is not created or worsened and the right heart may fill properly. In many cases this leads to the anastomoses being more technically challenging than what is encountered on-pump. It is important that the OPCAB surgeon retrain to become competent in creating high-quality anastomoses that are durable and achieve patency rates equivalent to those of anastomoses completed with CPB and an arrested heart. Methods to accomplish this are discussed later in this chapter.

## REENGINEERING

The motivation for adopting the OPCAB approach to surgical coronary revascularization should focus upon reducing complications while preserving excellent long-term outcomes. In evaluating whether to use a new technique in one's practice, it is important to identify the "drivers" that influence the decision. Inappropriate drivers probably will lead to failure of the reengineering process. Examples of inappropriate drivers include marketing, ambition, and excitement about a novel technique. In the authors' early experience with OPCAB, we did not have the proper motivation and for that reason did not perform more than about 10 percent of CABGs off-pump. Further, these cases were very stressful and unpredictable in light of the authors' desire to try out a new technique.

Coronary bypass surgery has achieved unparalleled long-term results that have been studied more extensively perhaps than the results of any other surgical procedure. Although surgeons have relied on this record to maintain patient referrals, the advent of drug-eluting intracoronary stents has produced excellent results as well. Percutaneous stenting, however, is associated with vastly reduced early morbidity and mortality. It was this realization that led the authors to the proper "driver" toward OCPAB surgery: the goal of eliminating early complications while maintaining the outstanding long-term results expected for CABG surgery. With this goal in mind, a technique was developed that minimizes risk for the patient at every possible step.

### Economic Impact

It is important to discuss the impact of the OPCAB approach on the real costs of surgical coronary revascularization. There are two methods by which OPCAB may influence cost. The first is a "production line" effect that involves eliminating over 50 CPB-related instruments as well as the CPB circuit and reducing operating room personnel (e.g., no perfusionist, fewer surgeons/nurses). A second effect is realized in terms of reduced morbidity as a consequence of the new technique. This effect (e.g., reducing stroke or renal failure rates) may apply only to a very small number of patients but constitutes a huge cost benefit. Combined, these effects lead to dramatic overall cost reductions once a complete reengineering toward OPCAB has been realized.

### Team Approach

A successful OPCAB program requires that all operating room staff (surgeons, anesthesiologists, and nurses) work together as a team with open lines of communication. This ensures that all members are able to anticipate each step and its potential complications so that they are prepared to correct any abnormalities. The authors also believe that it is essential for the surgeon and the anesthesiologist to engage in frequent collegial communication during the procedure so that both parties agree as each step in the operation is performed. This has the added benefit of producing a stress-free environment for all members of the operating team and leads to improved multidisciplinary care for the patient. If at any point and for any reason the anesthetist does not feel that the patient is stable enough to proceed, the manipulation is delayed until the hemodynamics have been optimized.

## SURGICAL TECHNIQUES

The authors' OPCAB technique has evolved over time. Since 1999, new devices have become available and the authors' experience with optimal anesthetic management and surgical manipulation has improved greatly. This goal of safe OPCAB and zero tolerance for conversion to CPB requires that every effort be made to ensure safety.

### Patient Conditioning

The first step in a successful OPCAB procedure begins before the incision is made. It is critical that the patient's hemodynamics be optimized to tolerate the stresses that surgical intervention will apply. To this end, patient hemodynamics must be "conditioned" adequately before any surgical manipulation of the heart. Thus, patients must have a normal heart rate [50–70 beats per minute (bpm)], normal systemic and pulmonary arterial pressures, normothermia, and normal electrolytes. For these reasons, monitoring in the authors' institution includes radial arterial catheterization, central venous and Swan–Ganz catheterization, and transesophageal echocardiography (TEE) for all OPCAB cases. TEE permits the detection of new wall motion abnormalities that may indicate early myocardial ischemia. PA monitoring is used to follow diastolic pressures as an early indicator of cardiac ischemia; alternatives include direct left atrial or pulmonary arterial pressure monitoring. It is the role of the anesthesiologist to adjust the patient's filling pressures to achieve pulmonary arterial diastolic (PAD) pressures between 10 and 15 mm Hg. In patients with certain preoperative conditions (e.g., atrial fibrillation, left ventricular hypertrophy), higher PADs are tolerated, reflecting the need for higher filling pressures. This is the exception, however, and the vast majority of patients will have the safest operation with PADs in the lower range. As will be described below, during most of the anastomotic period the heart lies outside the pericardium and the triangle of Einthoven, making detection of ischemia by electrocardiography (ECG) and TEE more difficult. Hence, the authors use the Swan–Ganz catheter as the primary mechanism to detect, treat, and follow this occurrence.

Another important role of the anesthesiologist is to optimize myocardial oxygen metabolism; this is achieved primarily by maintaining a normal heart rate. Patients are β-blocked adequately before surgery, with heart rates usually maintained around 60 bpm. However, if a patient has a heart rate greater

than 80 bpm, intravenous metoprolol is given to ensure that the heart is well protected from catecholamine surges. Any patient whose heart rate is below 60 bpm has atrial pacing wires placed and is paced atrially throughout the procedure. Atrioventricular sequential pacing is used for patients with additional conduction abnormalities. Oxygen demand is optimized through the strict avoidance of any inotropic medications, maintenance of filling pressures by leg elevation without Trendelenburg and volume infusion, and nitrates and $\alpha_1$-agonists as needed to optimize coronary perfusion pressure.

Serum electrolytes and acid–base balance also must be normalized to minimize triggers of arrhythmias. Serum potassium levels are checked hourly and repleted if they are less than 4.0 mEq/L as a protective measure against extrasystoles, atrial fibrillation, ventricular tachycardia, and ventricular fibrillation. In the authors' concept, extrasystoles [premature ventricular contractions (PVCs)] are considered abnormal and should never occur. When a PVC does occur, its etiology must be determined. The surgeon may have caused the PVC by touching the heart, and if this is the case, the anesthesiologist is notified and the operation proceeds. However, if the PVC was spontaneous, the patient's potassium level is checked. Levels below 4.0 mEq/L are repleted, but if they already are in the normal range, the abnormal beat is considered ischemic in origin until proved otherwise. The ECG–ST segments should be evaluated, as should the PA diastolic pressure and TEE for wall motion abnormalities. Only when all the members of the team are convinced that there is no ongoing ischemia does the operation continue. The authors have noticed, for instance, that a slightly misplaced stabilizer device may occlude coronary vessels, causing ischemia, which manifests as multiple PVCs. Only by adhering to these stringent principles can problems be identified and corrected in a timely fashion, avoiding hemodynamic compromise in the patient.

The patient's body temperature is regulated by two means. First, the room is kept warm until the patient is prepped and draped. Subsequently, it may be lowered to a comfortable temperature for the surgical staff. Second, a heated water blanket is placed underneath the patient and maintained at 40°C throughout the procedure. With these techniques, it is rare for a patient to leave the operating theater with a core temperature below 36.3°C.

## Incision

A median sternotomy is the incision of choice to perform OPCAB. This approach provides the most complete exposure for completion of all potential anastomoses while optimizing technical precision. Any coronary artery may be grafted with this exposure, and complex arterial reconstructions may be performed. Minimally invasive coronary artery bypass (MIDCAB) permits the use of a smaller minithoracotomy but is limited mainly to isolated revascularization of the anterior wall. More complex reconstructions are not possible. There also is concern that the quality of these anastomoses is reduced; this may translate into poorer long-term graft patency. For all these reasons, the authors strongly advocate a full median sternotomy for the optimal performance of OCPAB in all situations.

After the internal mammary artery (IMA) is mobilized from the chest wall, the pericardium is opened longitudinally, extending to the apex of the heart and completely along the diaphragm. The left pericardial edge is suspended from the retractor/drapes, but the right pericardial edge is left alone. This serves to rotate the heart slightly to the right, bringing the left anterior descending (LAD) artery closer to the midline of the operating field.

## Conduit Harvest

It is the standard of care to use at least one IMA for coronary revascularization. Usually the left IMA is harvested, but there are certain circumstances in which either right or bilateral IMA grafting is indicated. Patients with a patent dialysis shunt in the left upper extremity are at risk for a steal syndrome if a left IMA conduit is used. Also, an IMA should not be harvested ipsilateral to a subclavian artery stenosis. Patients with extensive atherosclerosis may benefit from angiography of the IMAs and the subclavian arteries during cardiac catheterization. For younger patients who are not diabetic, many surgeons choose to use both IMAs to provide two pedicled arterial grafts; this technique has demonstrated long-term patency. The specific technique for taking the IMA off the chest wall is beyond the scope of this chapter. The authors routinely open the pleura during IMA harvest, but this is a matter of surgeon preference. The authors routinely leave the right pleura intact and do not place the heart into the right chest.

A reversed saphenous vein is the most common conduit for the remaining grafts. This conduit is easy to harvest, is usually in good supply, is easy to work with, and has well-documented long-term patency in most situations. Newer techniques of endoscopic harvesting have further popularized the use of the saphenous vein because this technique reduces lower extremity wound complications and discomfort dramatically. This has now become standard practice for most coronary revascularization procedures requiring saphenous vein harvest.

Alternative choices for a conduit are generally more difficult to harvest, are often more difficult to work with, and have lower long-term patency rates. These choices include the lesser saphenous vein, the cephalic/basilic vein, a radial artery, the gastroepiploic artery, and cryopreserved vein. Only in situations in which conduit availability is severely limited should these other choices be considered.

## Anticoagulation

Anticoagulation consists of an intravenous heparin bolus administered at the completion of IMA harvesting to achieve

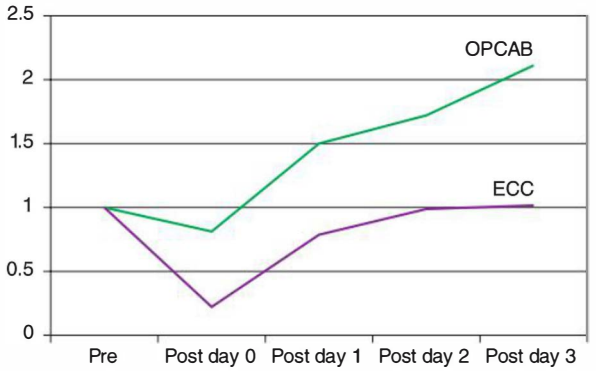



**FIGURE 28-2** Hypercoagulable profile of OPCAB patients. These data represent coagulation indices (CI) compared to baseline for patients undergoing standard CABG surgery (ECC group) compared with OPCAB. As expected, the group on-pump has a reduction of the coagulation index perioperatively (more likely to bleed) secondary to the effects of cardiopulmonary bypass. This returns to normal by POD#3. In contrast, the OPCAB group does not have a perioperative reduction in the CI but ends up being significantly hypercoagulable. These results were obtained by thromboelastography. (Data from Quigley RL, et al. Off-pump coronary artery bypass surgery may produce a hypercoagulable patient. *Heart Surg Forum* 2003;6:94–98. With permission from Forum Media Publishing.)

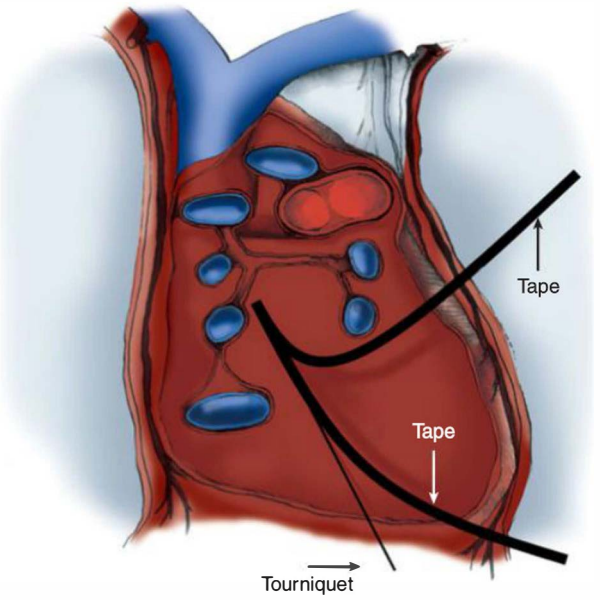



**FIGURE 28-3** Position of anchor stitch. The anchor stitch should be placed as far to the right side as possible, adjacent to the right inferior pulmonary vein. (With permission from Sergeant PL. Leuven, Belgium.)

a target activated clotting time (ACT) of 400 s or more; the heparin dose is usually 300 U/kg. ACT measurements are repeated every 20 min, and additional heparin is administered as necessary. Many authors routinely use a target ACT of 250 s despite a lack of evidence that this level is safe or prevents graft thrombosis. If the ACT level is too low to begin with or is not measured with adequate frequency, there is the potential for graft thrombosis. Furthermore, some data suggest that patients undergoing OPCAB have intrinsic hypercoagulable states (Fig. 28-2).[3] The authors feel that full-dose heparin should be used in all circumstances during the anastomotic period to maximize graft patency. Because OPCAB patients do not develop coagulopathies related to CPB, the authors feel strongly that performing vascular anastomoses with only partial anticoagulation confers a significant risk of thrombotic complications. Full protamine reversal is instituted at the completion of all anastomoses.

## Enucleation

In contrast to conventional CABG surgery, the left IMA to the LAD coronary artery is usually the first graft anastomosis performed in OPCAB procedures. This is the case because it is often the easiest to complete, requires minimal cardiac manipulation, and provides revascularization of the most critical myocardial region, conferring added protection from hemodynamic stability and arrhythmias during the remainder of the operation. The details of exposure for this anastomosis are described later in this chapter. After this step, the heart is enucleated from the pericardium so that the other coronaries may be visualized, stabilized, and grafted. This process is simple and consists of two parts.

First, a deep pericardial anchor stitch is placed with a long, heavy monofilament suture. The location of this stitch is of the utmost importance (Fig. 28-3). It should lie adjacent to the right inferior pulmonary vein, as far to the right as possible. This serves to lift the heart very effectively up out of the pericardium, bringing the atrioventricular groove closer to the surgeon. There has been much discussion in the literature regarding the use of various sling techniques[4,5] and we firmly believe this technique optimizes exposure with minimal risk if performed properly. Even more important, however, is the fact that this position prevents any distortion of the atrioventricular axis so that mitral insufficiency is not created or worsened if it is already present. A long sponge (opened up lengthwise) then is passed through the suture, and a tourniquet is advanced until the sponge is at the anchor stitch.

Second, the two "arms" of the sponge are used to lift the heart up and out of the pericardium. The assistant slowly pulls up and toward the patient's left with both arms of the sling, making sure to keep the mass of the heart supported (Fig. 28-4). It is critical that this step be performed slowly (about 2 mm with each cardiac contraction) to ensure stable hemodynamics. If at any time the filling pressures rise or the sponge appears to be constricting the left ventricle, the arms are lowered and the process is repeated. It is very unusual for any problems to occur during this procedure, and in fact, the authors have noticed that the heart functions in a superb

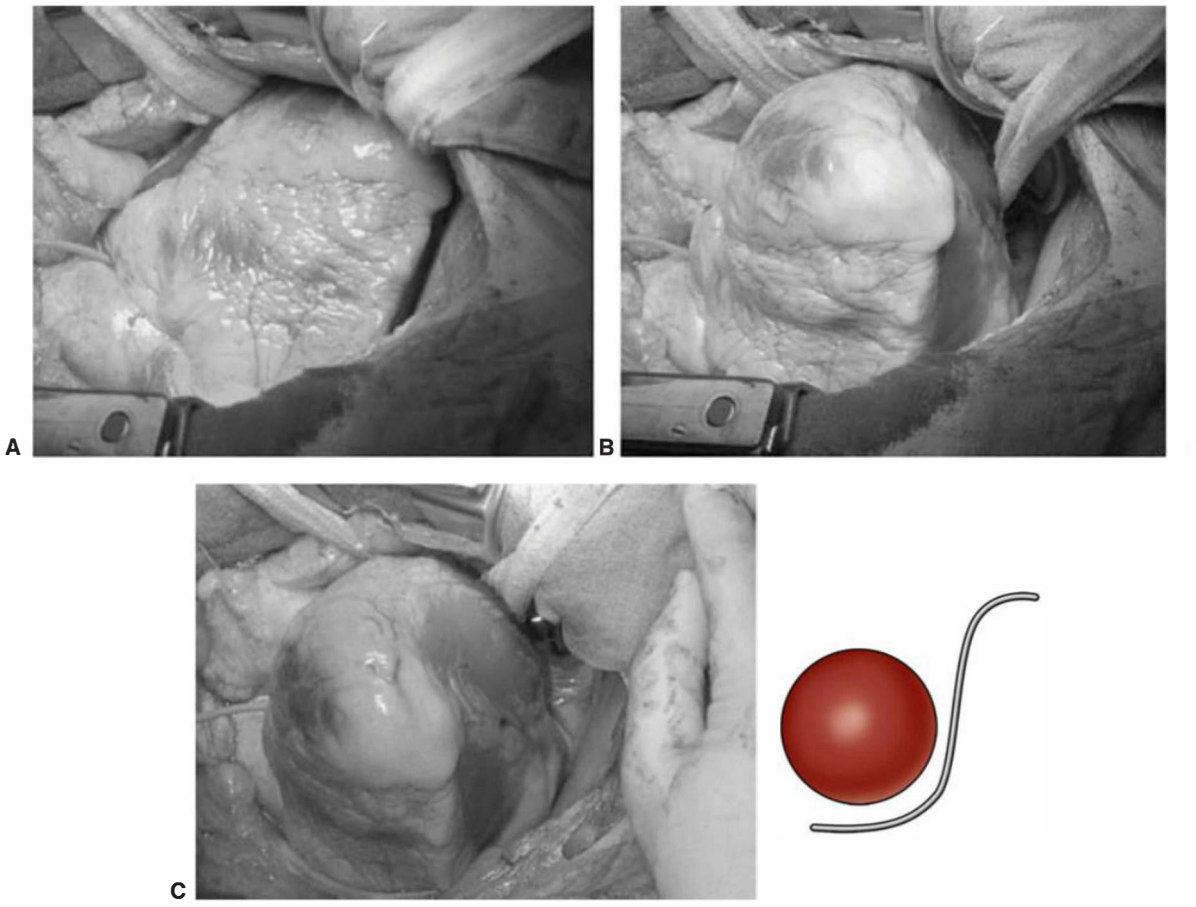



**FIGURE 28-4** Enucleation of the heart from the pericardium. As the arms of the sponge are pulled to the left, the heart rises out of the pericardium. This should be done slowly and should proceed without difficulty even with enlarged hearts or in patients with reduced ejection fractions. Note that the heart is globular and not in its normal configuration. (With permission from Sergeant PL. Leuven, Belgium.)

manner when elevated in this fashion. It is important after enucleation to readjust the right atrial filling pressures by means of leg elevation and volume infusion. The right ventricle should be inspected to make sure it does not distend as a result of malposition of the sling or the anchor stitch. Finally, the position of the sling on the left ventricular mass is checked and adjusted as needed; this may require subtle repositioning of the sling arms.

## Visualization

After successful enucleation, visualization is optimized in two steps: table rotation and apical suction. The operating table is rotated 30° toward the surgeon (the patient's right), ensuring that the patient's right leg is protected from falling by a secured padded block. A standard safety strap or belt would serve the same function. This table rotation causes the heart to move slightly toward the patient's right side, opening the space between the retractor and the lateral wall of the heart. Usually the circumflex marginal branches become visible after this step. It is important to remind the anesthesiologist to re-zero the pulmonary arterial catheter transducer after this maneuver.

Next, the apical suction device is placed near the ventricular apex in an area devoid of coronary vessels to prevent occlusive ischemia. Care must be taken to avoid the diaphragmatic surface of the heart, where the device may entrain air and become dislodged. With the apical suction device used in conjunction with the sling support, the authors have found that only 200 mm Hg of suction is required to maintain contact with the heart. This low degree of suction has the added benefit of reducing epicardial trauma. The function of the apical device is three fold: axial stabilization, reformatting of the ventricle, and axial displacement. Axial stabilization occurs once the device is secured in the desired position while preserving the ability of the heart for rotational contractility. After suction is applied to the apical suction device, the ventricular shape is reformatted from a globular to a more normal configuration by gently pulling the heart anteriorly. While the ventricle is maintained in its optimal configuration, the axis is displaced both superiorly

and to the patient's right (in the direction of the patient's right shoulder). This allows adequate exposure of lateral wall vessels while avoiding right-sided filling impairment from kinking or compression.

## Stabilization

The final preparatory step before the first coronary arteriotomy is made involves stabilization of the specific target coronary vessel. This has become much easier with the development of newer stabilizing devices over the last few years. These devices usually require 450 mm Hg of suction to stabilize the heart for a technically perfect anastomosis. In addition to the stabilizer, 4-0 braided sutures can be placed superficially in the epicardium adjacent to the coronary artery target and placed under gentle traction with hemostats to enhance the stabilization. A number of strategies may be employed in light of the particular anatomy confronted during this step. It is important not to apply suction directly over a coronary artery, however, as this may result in ischemia. A technique that often helps to prevent this problem involves placing bone wax in one or two of the suction holes that must lie atop a coronary artery.

Exposure of all target coronaries is identical with the exception of the LAD and the right coronary proximal to the take-off of the posterior descending artery. Because the LAD anastomosis is performed first, the sling support and apical suction are not placed initially. After the pericardium is suspended, additional horizontal sutures are placed along the lateral aspect of the left pericardium from cephalad to caudad, pulled anteriorly, and fastened to the surgical drapes. This rotates the heart about 15° toward the midline and brings the LAD into the middle of the operative field. At this point, target stabilization may proceed, followed by coronary shunting and completion of the graft anastomosis. In certain circumstances, diagonal vessels also may be revascularized using this exposure. However, if they lie more toward the lateral wall, the standard enucleation exposure is preferred.

The exposure of the right coronary proximal to the posterior descending coronary artery is also unique. Similar to exposure of the LAD, this is performed without the sling support or the apical suction device. Epicardial traction sutures are placed on the inferior wall near the acute margin and pulled in a cephalad direction, bringing the right coronary more anteriorly and into view. This allows for target coronary stabilization with a combination of the suction stabilizer and additional epicardial traction sutures (Fig. 28-5).

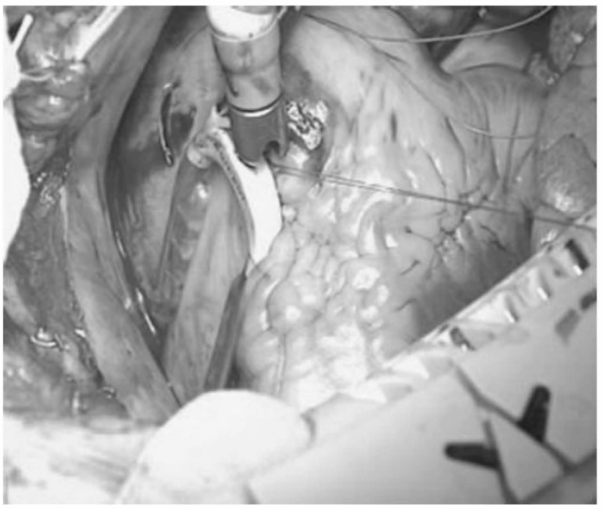


**FIGURE 28-5** Stabilization of the right coronary artery. This image demonstrates stabilization of the right coronary artery proximal to the posterior descending. Note the combination of epicardial traction sutures and target vessel stabilizer. There is no sling support for this exposure. (With permission from Sergeant PL. Leuven, Belgium.)

## Shunt Insertion

The primary objective of placing an intracoronary shunt during anastomotic construction is the avoidance or minimization of ischemia. Some surgeons never shunt, some do selectively, and some shunt with every anastomosis. The authors firmly believe in the third approach. The techniques described in this chapter are focused on reducing risk at every step to avoid hemodynamic instability and conversion to CPB. Thus, a shunt should be used for every anastomosis. The majority of coronary anastomoses probably can be completed safely without shunting. However, it is not possible to predict when shunting will be needed to avoid ischemic complications; thus, the only way to minimize risk fully is to shunt every time.

Flow through a shunt varies according to its internal diameter. All shunt sizes greater than 1.00 mm provide adequate blood flow to the distal coronary territory.[6] The maintenance of distal coronary flow has been further demonstrated to preserve myocardial function compared with temporary coronary occlusion.[7] This translates into a more stable operative environment, lower stress for the surgical team, and facilitates the construction of a technically perfect coronary anastomosis.

A frequently unmentioned advantage of placing intracoronary shunts is the improved visibility and exposure of the coronary artery walls. The shunt not only serves to keep blood out of the anastomotic area, it also keeps the vessel open to prevent suturing the back wall and improves visualization of the toe and heel areas. Furthermore, careful manipulation of the shunt can facilitate technically challenging anastomoses by opening space between the coronary wall and the shunt itself.

The main criticism of routine shunt placement during OPCAB is concern about endothelial damage; this concern is supported in the literature. For surgeons who choose not to shunt, the alternative is to occlude the coronary with Silastic slings and use a $CO_2$ blower/mister. However, when studies

have compared endothelial damage resulting from shunts with damage from vessel occlusion, shunts appear to be less traumatic.[8] In addition, the blower/mister device has been associated with severe complications, including endothelial damage and air embolism.[9,10] In considering all the risks and benefits of shunting for OPCAB, the authors believe the data firmly support the routine use of shunts to facilitate a safer procedure and the creation of technically perfect anastomoses.

Certainly, it also is reasonable to expect that the shunt insertion technique influences the degree of intimal disruption. The tip of the shunt should be placed in a "gooseneck" orientation rather than being pushed directly in, minimizing intimal trauma. The longer of the two shunt ends always is inserted first. The direction, whether proximal or distal, in which to insert the long end depends on the coronary anatomy. It should be placed away from coronary branches so that it will not lead to selective perfusion. These techniques are not part of routine surgical training, often need to be performed with the surgeon's nondominant hand, and can be challenging. For this reason, it is recommended that this technique be practiced in a model, re-creating the various angles and narrow spaces that will be encountered during OPCAB surgery. This enhances the surgeon's skill and ease at placing shunts so that the risks will be minimized during an actual operation.

## Distal Anastomoses

This is the final common step for each target vessel. For IMA conduits the authors recommend 8-0 polypropylene sutures and use 7-0 polypropylene for saphenous vein conduits. In the following paragraphs, a brief summary of the exposure and graft technique is given.

The LAD most often is revascularized first as it is the easiest to perform and, once completed, permits OPCAB to proceed more safely. Good exposure of lateral wall coronary targets requires that the heart be enucleated after placement of the deep pericardial anchoring stitch and sling support. Visualization is enhanced with table rotation and axial stabilization/displacement with the apical suction device, facilitating stabilization of the circumflex marginal vessels, although in a somewhat narrow space (Fig. 28-6). This space can be optimized by refinements in positioning the axial stabilizer, further widening of the sternal retractor, and adjustment of the vessel stabilizer itself. Opening of the right pleura with placement of the heart in the right chest is not only unnecessary but potentially harmful if venous return is impeded.

The inferior wall vessels (posterolateral and posterior descending arteries) are performed similarly, usually after completion of the lateral wall grafts. The heart is enucleated and apical suction is applied with displacement of the heart superiorly and to the right. This brings the inferior wall into a vertical alignment away from the diaphragm and allows for target vessel stabilization. The exposure of the right coronary proximal to the posterior descending (mid-right coronary artery) has been described and does not require enucleation or apical suction (Fig. 28-5).

## Proximal Anastomoses

Standard techniques of partial aortic occlusion for construction of the proximal graft anastomoses have mostly been discarded due to the increased aortic manipulation and corresponding embolization risk. Clampless devices have been developed and improved, which allow for safe and effective proximal vein anastomosis to the aorta. These connections are completed with 6-0 polypropylene suture in the standard fashion and will not be discussed further here.

## Revascularization Strategies

A frequent criticism of OPCAB is that fewer anastomoses are performed, especially on the lateral wall. In inexperienced hands this may be true, but with a technique that is safe and effective, all potential coronary targets should be accessible. Multiple studies demonstrate that all coronary targets are accessible with current off-pump techniques. Furthermore, there is evidence that suggests selection bias may play a role in fewer grafts being performed in OPCAB versus traditional CABG.[11] In other words, patients requiring fewer grafts are more likely to be chosen as OPCAB candidates.

The performance of OPCAB also does not preclude the surgeon from completing an all-arterial revascularization. In contrast, the concept of reducing complications while maximizing benefit in OPCAB is concordant with this strategy, and it is technically feasible to do so. Unless a patient is extremely morbidly obese or older than age 80 years, the authors prefer to use bilateral IMAs with the right mammary artery being a free graft, sequentially grafted around the lateral and inferior walls. Since the authors' transition to OPCAB surgery, the percentage of arterial anastomoses and all-arterial revascularization has increased dramatically.

At KU Leuven, the authors avoid all manipulation of the aorta whenever possible to reduce the risk of embolic stroke. For this reason, the standard coronary revascularization scheme consists of the left IMA grafted to the LAD and a free right IMA graft taken off the proximal left IMA and sequentially anastomosed around the lateral and inferior walls. If there is a contraindication for the use of bilateral IMA grafts, the saphenous vein is used. In an elderly patient with significant comorbid conditions and a good-quality small-caliber vein, this also may be taken off the proximal left IMA before being sequenced around the lateral and inferior walls. When the left IMA is used as an inflow source for a free graft, the anastomosis is placed as proximal on the left IMA as possible, where the vessel caliber is maximal; a shunt also is placed to ensure a technically perfect anastomosis. There has been no increased incidence of LIMA-to-LAD graft failure as a

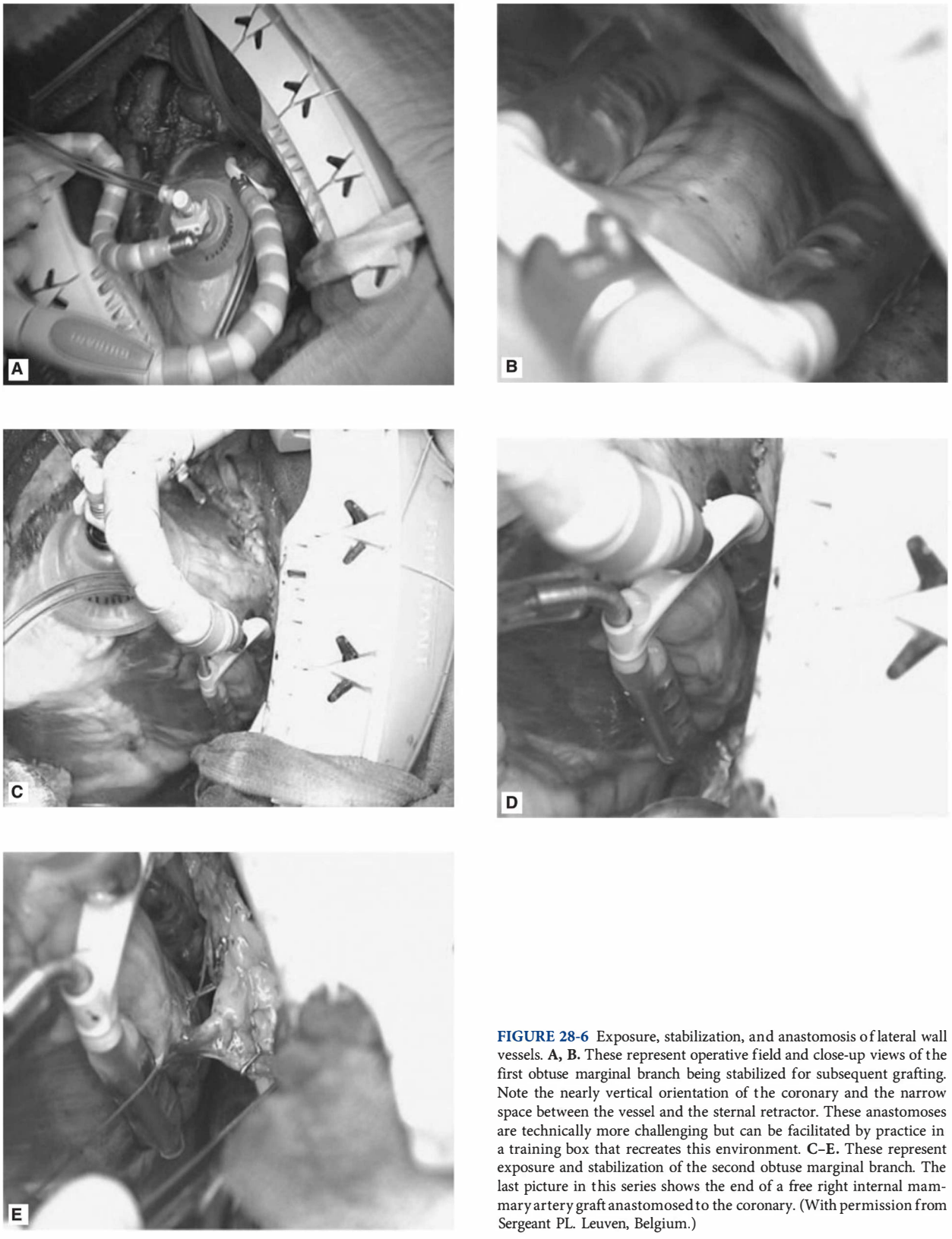



**FIGURE 28-6** Exposure, stabilization, and anastomosis of lateral wall vessels. **A, B.** These represent operative field and close-up views of the first obtuse marginal branch being stabilized for subsequent grafting. Note the nearly vertical orientation of the coronary and the narrow space between the vessel and the sternal retractor. These anastomoses are technically more challenging but can be facilitated by practice in a training box that recreates this environment. **C–E.** These represent exposure and stabilization of the second obtuse marginal branch. The last picture in this series shows the end of a free right internal mammary artery graft anastomosed to the coronary. (With permission from Sergeant PL. Leuven, Belgium.)

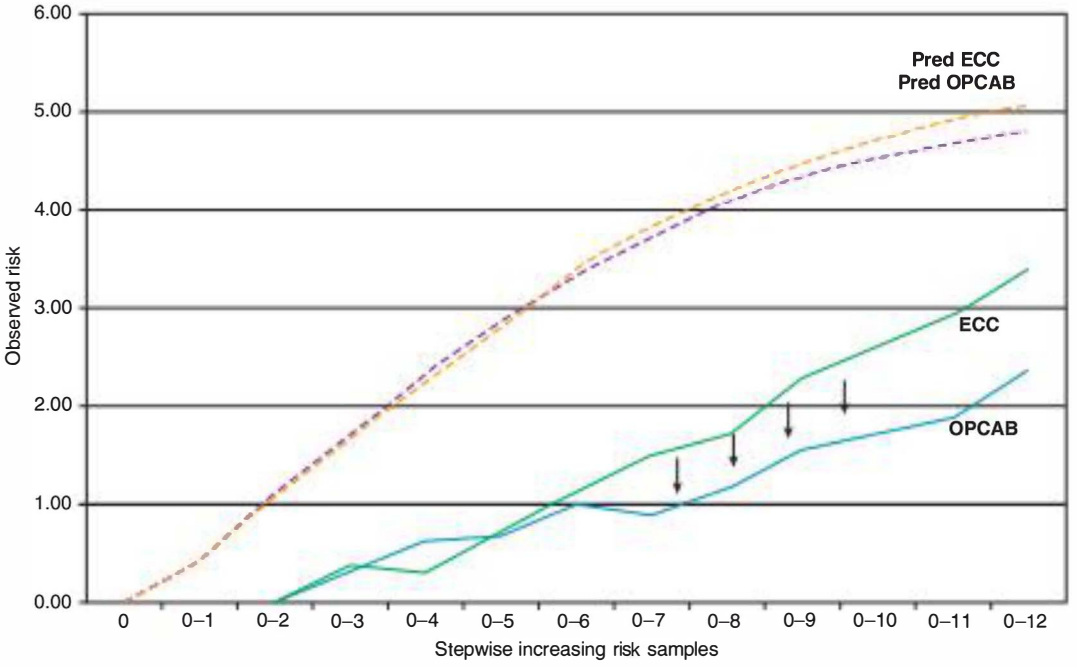



**FIGURE 28-7** Comparison of expected to observed mortality. This graph shows that patients with CABG on-pump (ECC) have much better mortality than predicted on the basis of risk. Observed mortality in OPCAB patients is even better than that for the ECC group in patients with increasing risk. Note: Expected mortality was the same for both groups. (With permission from Sergeant PL. Leuven, Belgium.)

consequence of this strategy. In some cases, though, there is no alternative to placing a graft on the ascending aorta. In this situation, the surgeon should avoid placing a partial occlusion clamp by using novel technologies such as HeartString or other connector devices that are less likely to shower emboli.

# OUTCOMES

## Literature

It is important to remember that in reviewing the literature regarding a specific surgical technique, the data represent the specific technique described and must be powered adequately for the reader to draw conclusions. It is easy to make any technique appear unsuccessful if it is performed by inexperienced surgeons or if the components of the operation are not the most effective. Furthermore, outcomes cannot be evaluated if the specific technique does not incorporate all measures to minimize risk. Conclusions pertain only to the exact circumstances that existed in the study.

Although there are certain reports, which seem to indicate less than ideal outcomes with OPCAB compared to standard CABG, the preponderance of evidence in the surgical literature clearly demonstrate overall improved mortality, morbidity, and cost with OPCAB.[12–15]

## Mortality

A number of studies have documented a significant improvement in mortality in OPCAB patients compared with on-pump CABG,[16] as do data from KU Leuven (Fig. 28-7). Risk cannot be reduced where none is present. Therefore, low-risk patients tend not to have a mortality benefit from OPCAB. However, for patients with increasing risk, here defined by Euroscore, the improvement in mortality, both in-hospital and at 3 months is substantial. There is also a much more significant reduction in expected-to-observed mortality with OPCAB compared with conventional CABG.

## Morbidity

Avoidance of CPB and its associated complications tends to result in improvements in outcomes for all organ systems. Below is a summary of the literature pertaining to this along with data from KU Leuven.

### NEUROLOGIC

This category includes two distinct areas of injury: stroke and neurocognitive dysfunction. Stroke is a more clearly defined outcome, and because of its low incidence, it is difficult to demonstrate an improvement without very large patient cohorts. Nonetheless, various studies in the

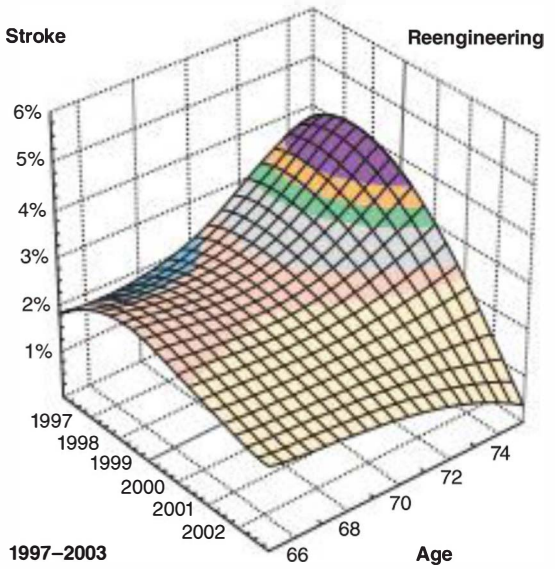



**FIGURE 28-8** Stroke rate in high-risk patients. These data represent patients with preoperative carotid stenosis greater than 80 percent. This cohort consists of 200 patients in each group and achieves statistical significance ($p = 0.02$) with a relative risk reduction of 68 percent. (With permission from Sergeant PL. Leuven, Belgium.)

literature have demonstrated either equivalent or reduced stroke rates for patients undergoing OPCAB compared with those receiving on-pump CABG. This beneficial effect may be somewhat mitigated in patients who have a history of preoperative neurologic events.[17] Similarly, data from KU Leuven show that intraoperative stroke essentially has been eliminated by the routine performance of OPCAB. Furthermore, data now also demonstrate significant improvement in stroke by utilizing "no-touch" OPCAB techniques, avoiding any clamping or manipulation of the ascending aorta.[18,19] Postoperative strokes still occur as a result of hypotension and atrial fibrillation with cerebral embolization. Lower stroke risk is also evident when stroke is stratified according to patient age. These data become statistically significant when patients at high risk for stroke are compared (Fig. 28-8).

## PULMONARY

This category often is represented by the "time to extubation" metric. Many OPCAB centers have demonstrated significantly reduced extubation times that translate into shorter lengths of stay in the intensive care unit (ICU).[20] Furthermore, a number of reports have advocated the safe extubation of OPCAB patients in the operating room at the conclusion of the procedure.[21]

## CARDIAC

These complications can be separated into myocardial infarction (MI) and enzyme release not associated with acute infarction. Graft failure also can be included in this subsection because acute graft occlusion often leads to infarction. Although many studies have demonstrated no difference in the incidence of perioperative MI with OPCAB, some authors have found a reduction in this event in patients undergoing OPCAB.[16] Logic dictates that avoiding ischemic cardioplegic arrest will reduce myocardial injury during CABG procedures. Data from KU Leuven do not reveal any reduction in the incidence of MI in OPCAB patients.

The significance of elevated troponin values after OPCAB remains uncertain. Certainly, no data about the "normal" levels of troponin after this procedure are conclusive. A few studies have investigated enzyme release after OPCAB,[22] and the results seem to indicate a trend toward reduced troponin levels but no specific correlation with reduced infarct rates.

Graft failure rates with OPCAB generally seem to be equivalent to those for conventional on-pump CABG.[23] One article that placed international focus on poor graft patency in OPCAB[24] demonstrated only that the specific technique used by those authors and performed by those surgeons was less than satisfactory. This finding should not be generalized to a belief that all OPCAB procedures are doomed to similarly poor outcomes with respect to graft failure. Only by minimizing risk and maximizing safety (e.g., full anticoagulation, use of intracoronary shunts) can the full benefits of OPCAB be realized.

## RENAL

Perhaps the area of greatest benefit in OPCAB patients is the renal system. Patients with preexisting renal dysfunction who undergo conventional CABG have a significant propensity for postoperative renal complications, including temporary or permanent hemodialysis. For patients with normal kidney function, the risks are quite low, and thus OPCAB results suggest no benefit. However, in high-risk cohorts it has been proved clearly that avoiding CPB leads to dramatically reduced renal complications.[25] OPCAB also seems the more appropriate technique for patients already requiring dialysis prior to their operation in terms of reducing blood transfusions, MI, and hospital mortality.[26] This is in agreement with data from KU Leuven, which have shown a 26-percent reduction in the relative risk for postoperative hemodialysis or ultrafiltration.

## HEMATOLOGIC

The literature supports the notion that OPCAB patients experience less blood loss from surgery in addition to having lower transfusion requirements. This results from increased thrombin generation and reduced fibrinolysis in the presence of intact, functioning platelets. Various authors have hypothesized about ideal antiplatelet regimens to prevent postoperative thromboembolic complications in OPCAB patients. There also appears to be a protective effect against gastrointestinal ischemia by avoiding CPB in these patients.[27]

### LENGTH OF STAY

The performance of OPCAB has been shown to reduce the length of stay of cardiac surgical patients. This probably is a result of reduced systemic inflammation, decreased fluid requirements, and quicker time to extubation. Furthermore, lower morbidity rates also lead to earlier patient discharge from the hospital. Evidence from KU Leuven supports these findings as well, especially when patients are stratified by age or Euroscore.

### COST

Economic savings in OPCAB patients are realized by two means: (1) small, production-line advantages that result from every patient undergoing surgery (e.g., reduced operating room charges, reduced personnel charges) and (2) large savings in a small number of patients who avoid severe complications (e.g., reduced incidence of stroke and renal failure). Therefore, OPCAB can lead to dramatic cost savings. The literature continues to support this claim.[28]

### RACE/GENDER

Historical data on OPCAB outcomes by race and gender have been limited. Newer studies, however, have been more successful in identifying whether OPCAB can influence morbidity and mortality in females and minorities specifically. OPCAB has now been shown to be a safe and effective modality for both low- and high-risk female patients. However, when late outcomes are compared by gender, women seem to have only equivalent, or perhaps higher, complication rates as men.[29]

Data now available for African American patients seem to suggest that short- and long-term outcomes remain worse than for Caucasian patients, even when OPCAB is performed.[30]

## SUMMARY

OPCAB is much more than a simple alternative to conventional CABG surgery without the assistance of CPB. It is a concept that emphasizes patient safety and long-term benefit. To achieve this, a multidisciplinary approach must be employed, involving nursing, anesthesia, and surgery. When all efforts are made to minimize risk and provide a stress-free operating room environment, great benefit for the patient may be achieved. Although there is some disagreement in the literature about short- and long-term outcomes with OPCAB, one must be cognizant of the specific techniques used and the experience of the surgeons involved in a study. There is surely more than one successful OPCAB technique. With perseverance and diligent training and retraining, OPCAB should become applicable to the entire spectrum of patients presenting for surgical coronary revascularization.

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## OFF-PUMP CORONARY ARTERY BYPASS BOARD REVIEW QUESTIONS (CHAPTER 28)

1. The primary goal of OPCAB is:
   A. Achieving the greatest number of grafts
   B. Performing all-arterial grafting
   C. Reducing cost of CAB
   D. Decreasing morbidity and mortality
   E. Increasing patient referrals

2. Which of the following settings is most appropriate for OPCAB?
   A. Elective
   B. Acute MI with cardiac index less than 1 L/min/$m^2$
   C. Pulmonary edema with cardiac index between 1 and 2 L/min/$m^2$
   D. None of the above
   E. All of the above

3. Which of the following is true regarding anticoagulation for OPCAB?
   A. Full-dose heparin (300 units/kg) should be used.
   B. ACT should be maintained around 250 s.
   C. Repeat ACT should be performed every 20 min.
   D. A and C
   E. All of the above

4. Intracoronary shunts should be used according to which of the following criteria?
   A. Rarely due to high risk of endothelial damage
   B. Selectively based on arterial size
   C. Selectively based on artery location
   D. Selectively based on ischemia during vessel occlusion
   E. Routinely after thorough simulator training

5. Which of the following is true regarding outcomes after OPCAB?
   A. Statistically significant results are often achieved even with relatively small patient cohorts
   B. OPCAB confers a higher intraoperative risk of stroke
   C. "No-touch" technique on the aorta has been repeatedly shown to reduce stroke
   D. Atrial fibrillation and hypotension both contribute to intraoperative stroke
   E. There is no statistically significant improvement in stroke when high-risk patients are compared.

## ANSWERS

1. **Answer: D.** The primary goal of coronary artery bypass grafting, whether with or without cardiopulmonary bypass, is to reduce morbidity and mortality from coronary artery disease.
2. **Answer: A.** Certain clinical conditions warrant the use of cardiopulmonary bypass, including patients undergoing CPR, acute myocardial infarction with low cardiac index, and pulmonary edema with reduced cardiac performance.
3. **Answer: D.** Full dose heparin should be used and the ACT should be maintained at above 400 s. A lower ACT may be associated with a higher risk of graft failure in the setting of OPCAB. The ACT should be repeated every 20 min.
4. **Answer: E.** Following the principle of minimizing risk, shunts should be routinely placed for every anastomosis. Improper placement can cause endothelial damage and it is recommended that surgeons have thorough training and practice using a simulator model to reduce the risk of shunt placement.
5. **Answer: C.** Only the "no-touch" technique has been conclusively shown to reduce stroke. In general, large cohorts of patients are required to demonstrate statistical significance, as stroke is an uncommon event.

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# Reoperative Coronary Artery Bypass Surgery

*Christopher J. Barreiro*
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## KEY CONCEPTS

- Epidemiology
  - Among the 200,000 coronary bypass operations performed annually in the United States, reoperative coronary artery bypass surgery (redo-CAB) accounts for approximately 5 percent of all isolated coronary artery bypass grafting (CABG) procedures. Recent data from the Society of Thoracic Surgeons database show that there has been a decrease in the number and percentage of redo-CAB procedures (2000, $N = 8929$, or 6.1 percent; 2009, $N = 8189$, or 4.3 percent).
- Pathophysiology
  - Reoperative coronary artery surgery is performed for patients in whom there is definite demonstrated myocardial viability with associated symptomatology. A multivariate analysis demonstrated that preoperative angina, use of vein grafts only, previous myocardial infarction, incomplete revascularization, female gender, and smoking at a younger age were independent risk factors for recurrent angina and a potential need for reoperation.
- Clinical features
  - In more recent years, the reoperative candidate population has evolved to include older patients, with diminished left ventricular function, triple-vessel coronary artery disease (CAD), and graft failure becoming the predominant etiologic factors. Recently, however, there appears to be an increase in number of reoperative candidates with progression of their native disease distal to their patent conduit graft sites.
- Diagnostics
  - Diagnostic tests include those used to assess viable myocardium and those used for planning the operation. The tests frequently used for detecting viable myocardium include thallium scintigraphy, dobutamine echocardiography, magnetic resonance imaging, and positron emission tomography. Coronary angiography is the gold standard for determining the need for revascularization and the appropriate targets. Standard computed tomography (CT) can be used to assess the substernal structures. However, with the development of multislice CT and three-dimensional (3-D) reconstruction, accurate pictures of the cardiac anatomy and the relationships of bypass grafts to mediastinal structures as well as the sternum can be demonstrated vividly.
- Treatment
  - Reoperative surgery for CAD requires knowledge of mediastinal structures and a staged entry into the chest with the use of an oscillating saw and scissors for division of the outer and inner tables, respectively. Femoral artery and vein cannulation may be necessary if it is anticipated that cardiac structures are in jeopardy of being injured upon reentry. Careful dissection in the area of previous vein grafts that may be atherosclerotic is important, as downstream debris from these vein grafts is the most common cause of mortality in this high-risk group of patients.

## INTRODUCTION

Coronary artery bypass grafting (CABG) is the most common cardiac surgical procedure, with nearly 200,000 operations performed annually in the United States according to the Society of Thoracic Surgeons (STS) database. Reoperative CABG accounts for approximately 5 percent of all isolated CABG procedures and is often the result of graft failure, progression of native coronary disease, or incomplete revascularization.[1,2] Recent STS data show that there has been a decrease in the number and percentage of isolated redo-CABG operations (2000, $N$ = 8929, or 6.1 percent; 2009, $N$ = 8189, or 4.3 percent). There are probably many reasons for this trend, including improved medical management and interventional cardiology. Most redo-CABG procedures today are performed more than 10 years after the primary CABG, and are technically more challenging because of the difficulty of sternal reentry, the presence of patent bypass grafts, and limitations of potential bypass conduits. In addition to the technical complexities, the risk profile of reoperative candidates continues to increase. Redo-CABG patients are older, have greater extent of coronary artery disease (CAD), and have worse left ventricular (LV) function. However, these obstacles have been offset by improvements in operative techniques and perioperative care, resulting in improved survival and postoperative outcomes in redo-CABG patients.

## CLINICAL FEATURES

Surgical reintervention rates and recurrent symptoms are two of the primary outcomes used to gauge the success of the initial CABG procedure. In two large cohort studies, freedom from redo-CABG at 1, 5, 10, and 15 years was 99, 97, 89, and 72 percent, respectively.[2,3] In addition, freedom from recurrent angina after initial CABG surgery has been approximately 80 percent at 10 years.[4] In a multivariable analysis, preoperative angina, use of vein grafts only, previous myocardial infarction (MI), incomplete revascularization, female gender, smoking, and younger age were found to be independent risk factors for recurrent angina.[5] Another large study defined diffuseness of CAD using a validated diffuseness score, and found that diffuse CAD was an independent predictor of morbidity and mortality.[6]

Reoperative candidates include patients with recurrent symptoms and jeopardized viable myocardium due to progression of CAD or graft failure. Predictors of redo-CABG include young age at initial operation, male gender, worse symptom severity, absence of internal mammary artery (IMA) grafts, incomplete revascularization, impaired functional status, and multivessel disease.[7,8] Initially, incomplete revascularization or worsening atherosclerosis of the native coronary arteries accounted for the majority of redo-CABG operations. As the redo-CABG population has evolved to include older patients with worse LV dysfunction and triple-vessel disease, graft failure has become the predominant etiologic factor. More recently, however, there has been an increase in the number of reoperative candidates with progression of their native disease distal to patent arterial graft anastomoses.[8]

Choice of graft conduits at the primary operation has been shown to be a significant factor in determining the need for reoperation. The increased use of arterial conduits, including IMA and radial artery grafts, instead of saphenous vein graft (SVG) conduits, has reduced the rate of reoperation significantly in recent years. IMA patency rates after primary CABG surgery exceed 90 percent at 10 years; in contrast, SVGs begin to deteriorate rapidly after 5 years and have a 50 percent patency rate at 10 years.[9] Furthermore, nearly 20 percent of SVGs occlude by 1 year.[10] Although some debate remains, there are several large retrospective studies that support improved survival in patients receiving total arterial revascularization, in both primary and redo-CABG procedures.[11] Because of improved patient survival and patency rates of arterial grafts, the IMA has become the choice conduit—when available—for primary CABG as well as for redo-CABG surgery for SVG stenosis.

Early SVG stenosis within the first year of primary CABG often is due to intimal hyperplasia. The increased intimal thickness presumably is due to exposure of the vein to systemic arterial pressures. This proliferative process results in vein graft atherosclerosis, which is the leading cause of late occlusion and accelerates dramatically after 5 years. SVG atherosclerosis has a worse prognosis than does native vessel atherosclerosis. The lesion in a vein graft is often diffuse and prone to plaque rupture, with increased rates of thromboembolic phenomena. As a result, even minimal manipulation of SVGs or antegrade cardioplegia during redo-CABG surgery can dislodge atheromatous emboli and result in MI. This represents the most common cause of operative mortality in patients undergoing redo-CABG surgery. Arterial grafts are much less prone to occlusion, although they can develop neointimal proliferation, most commonly at the distal anastomotic site.

## PREOPERATIVE CONSIDERATIONS

Preoperative planning is of even greater importance in redo-CABG surgery than it is in primary procedures. For the reoperation to occur safely, adequate preoperative assessment and analysis are critical (Table 29-1). The patient's history must be reviewed thoroughly, with close attention not only to all previous cardiac surgery, but also to any relevant

**TABLE 29-1: Preoperative Assessment**

| | |
|---|---|
| Chest x-ray | Thallium scintigraphy |
| Computed tomography | Dobutamine echocardiography |
| Coronary angiography | Magnetic resonance imaging |
| Positron emission tomography | Vascular Doppler imaging |

procedures or comorbidities that may affect the surgeon's approach to the reoperation. For example, a patient with a previous history of mediastinitis should be considered for a thoracotomy incision as an alternative to redo-sternotomy if the coronary anatomy is favorable for this approach. Medications should be reviewed carefully so that any drugs affecting platelet function or coagulation can be discontinued at least 1 week prior to the operation. Most importantly, it is essential to have a clear and complete understanding of the patient's native coronary and bypass graft anatomy before undertaking a reoperation. This information can be ascertained from previous operative records and coronary angiograms. The surgeon must also determine if bypassing potentially graftable vessels will improve perfusion to viable regions of myocardium. In addition to determining the feasibility of beneficial revascularization, adequate bypass conduits must be available.

## Bypass Conduits

The surgeon should have a preoperative plan for the selection of bypass conduits. Venous Doppler studies often are used to determine the adequacy of saphenous vein segments. Vein mapping is a simple, accurate, and noninvasive method to predict the course of the vein and identify venous anomalies. On occasion, venous mapping can influence the surgeon's choice of the venectomy site. Arterial Doppler studies can assess the radial arteries. In addition, an Allen's test can help ensure that digital perfusion will remain adequate if the radial artery is harvested as a potential conduit. Abnormalities in the IMA also can be detected with Doppler studies. IMA ultrasound studies may reduce the need for invasive preoperative assessment of patency and length, and allow for postoperative assessment of coronary artery flow reserve. However, IMA angiography provides a more complete evaluation of these arteries and should be used whenever possible.

# DIAGNOSTIC MODALITIES

## Chest X-ray and Computed Tomography

The surgeon can evaluate the risk of sternal reentry by means of radiography. A posteroanterior and lateral chest x-ray can give the surgeon an idea of the proximity of important cardiac structures to the sternum. Steel clips that are visible on a chest radiograph also can be used to trace the path of patent IMA grafts. If deemed necessary, CT offers an enhanced view of substernal structures. CT scans can determine the size and position of cardiac chambers as well as the course of bypass conduits. This information can guide sternal reentry. In a series of 167 redo-CABG patients, high-risk findings by preoperative CT imaging led to more frequent adoption of preventive surgical strategies.[12] In patients at high risk for hemorrhage or injury to substernal structures, femoral dissection should be performed to allow for peripheral and expeditious institution of cardiopulmonary bypass (CPB). Alternative incisions should be considered if they are deemed necessary on the basis of this evaluation. In addition to standard CT scanning, intravenous angiography multislice CT and 3-D reconstruction is a recent technological advancement that has been found to be extremely accurate in detecting CABG patency and occlusion (Fig. 29-1).[13] This imaging modality also provides clear and accurate pictures of the cardiac anatomy and the relationships of bypass grafts to mediastinal structures; however, standard angiography remains the modality of choice for assessing native coronary circulation (Fig. 29-2).

## Coronary Angiography

Coronary angiography is a necessary step in the complete preoperative assessment of potential redo-CABG patients. To gain a better understanding of the patient's coronary anatomy, previous angiograms and operative notes should be reviewed and are invaluable tools for the reoperative surgeon as well as the interventional cardiologist performing the angiogram. The coronary angiogram can be used to estimate the severity of atherosclerotic and thrombotic lesions. The severity of native coronary and SVG stenosis often is underestimated on the basis of a single angiographic view. Therefore, multiple projections are required to visualize the entire native coronary circulation as well as the previously constructed bypass grafts. The angiogram also can aid in determining the presence of graftable target vessels. To ensure that this is performed accurately, the angiographer must inject all relevant branches and allow enough time for the filling of the coronaries by collaterals. It is important that angiography supplement the surgeon's intraoperative assessment of the patient's coronary anatomy.

## Assessing Viable Myocardium

Impaired LV function secondary to ischemic heart disease is not always permanent, and may improve considerably with revascularization. Restoration of blood flow to chronically underperfused and ischemic myocardium often can restore contractile function. However, revascularization of scar tissue will not result in functional improvement. Given the considerable operative morbidity and mortality for patients with LV dysfunction undergoing surgical revascularization, especially redo-CABG, it is essential to differentiate between viable and nonviable myocardium. Several noninvasive imaging modalities are used to identify physiologic markers of myocardial viability in regions with contractile dysfunction. The most commonly used techniques to ascertain viability include positron emission tomography (PET), thallium scintigraphy, dobutamine echocardiography, and cardiac magnetic resonance imaging (cMRI). PET is an established method for demonstrating preserved

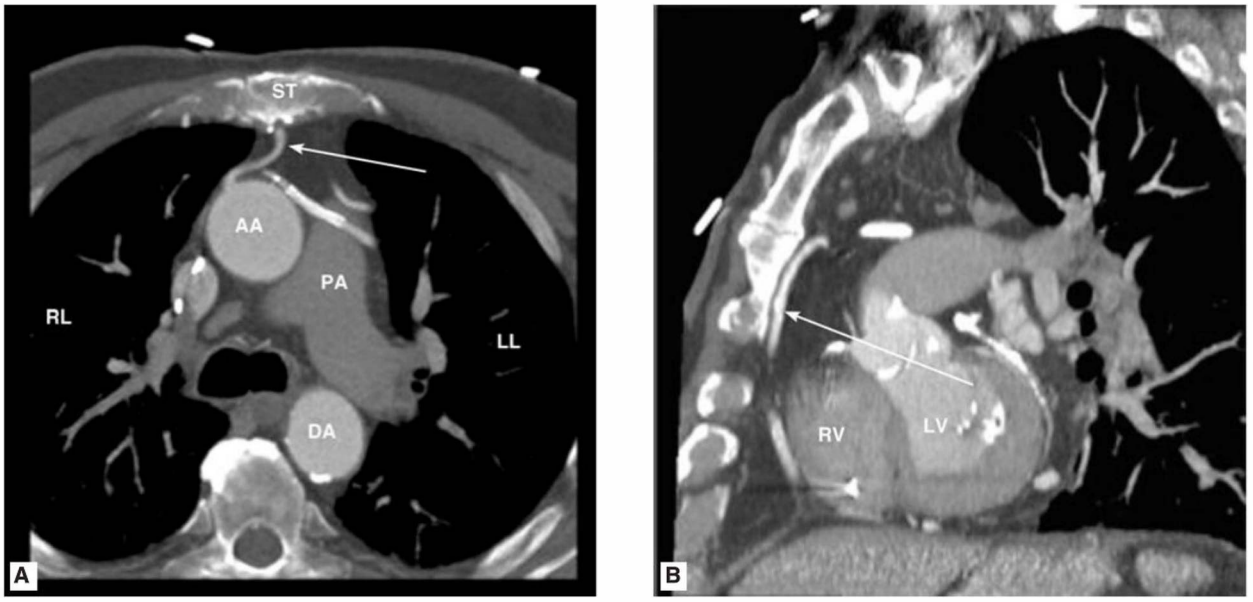



**FIGURE 29-1** **A.** Axial views of a contrast-enhanced multidetector computed tomographic angiography (MDCTA) of the chest demonstrating an adherent aortocoronary graft (arrow) to the underside of the sternum. AA, ascending aorta; DA, descending aorta; LL, left lung; PA, pulmonary artery; RL, right lung; ST, sternum. **B.** Sagittal views of a contrast-enhanced MDCTA of the chest demonstrating an adherent aortocoronary graft (arrow) to the underside of the sternum. LV, left ventricle; RV, right ventricle. (Reprinted from Kamdar AR, et al. Multidetector computed tomographic angiography in planning of reoperative cardiothoracic surgery. *Ann Thorac Surg* 2008;85(4):1239–1245. With permission from Elsevier.)

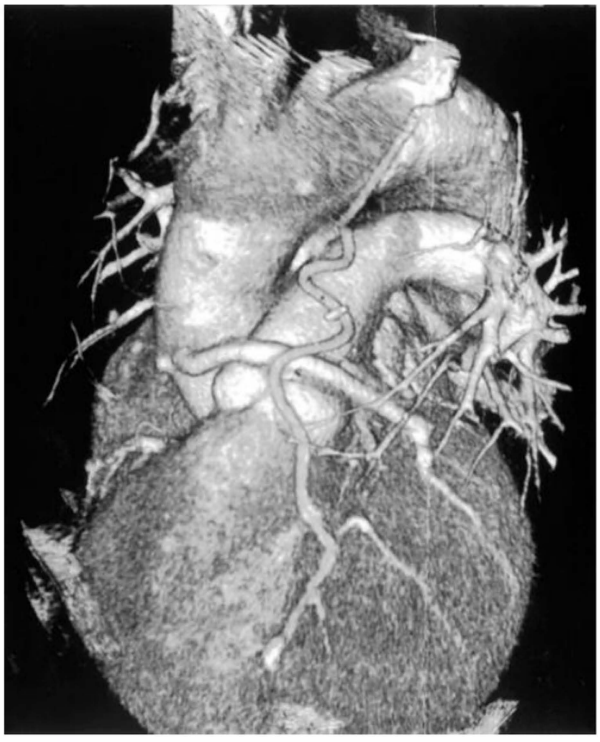


**FIGURE 29-2** Multislice computer tomography illustrating the relationship of the internal thoracic artery and saphenous vein graft to other cardiac structures.

metabolic activity through the use of $^{18}$F-fluorodeoxyglucose as a marker of myocardial glucose utilization. Thallium scanning is used to assess myocardial perfusion and membrane integrity, whereas the myocardial contractile reserve is best evaluated by using dobutamine echocardiography or cMRI. The chief advantage of cMRI is the ability to simultaneously detect ischemic myocardium, calculate ventricular chamber size and volumes, and assess viability and scar formation.[14]

## MEDICAL THERAPY

### Nonsurgical Interventions

Redo-CABG carries with it significantly higher morbidity and mortality as compared with patients without a history of CABG. Therefore, various nonsurgical approaches to revascularization, such as percutaneous coronary interventions (PCI) with intracoronary stenting have become much more widespread in recent years. As the line begins to blur between candidates for surgical versus nonsurgical revascularization, many studies have been performed to compare these two techniques for primary revascularization. However, the data are more limited in patients in need of reintervention who already have undergone CABG. The AWESOME trial was a nationwide, prospective, multicenter effort, which demonstrated that PCI is a viable alternative for patients with medically refractory myocardial ischemia and risk factors for adverse outcome with CABG. This registry demonstrated

that for the specific subset of patients with prior CABG, both the physicians and patients chose PCI by a 2:1 margin, and a survival advantage with PCI was shown in the patient-choice cohort. For the 142 randomized patients to either redo-CABG or PCI, similar survival results were found with an overall 3-year survival of 76 and 73 percent, respectively.[15] However, redo-CABG is associated with greater success in providing complete revascularization as well as a reduced need for subsequent revascularization procedures. In a review of patients referred for reoperation versus PCI at the Cleveland Clinic, those undergoing redo-CABG were more likely to be male and have diabetes, hypertension, valvular disease, and severe LV systolic dysfunction. These patients generally had fewer functioning venous and arterial grafts and a larger region of myocardium in jeopardy. Although reoperation is associated with a higher risk of in-hospital complications than is PCI, it has potential long-term benefit when there is a lack of functioning bypass grafts or a lack of a patent arterial graft to the left anterior descending (LAD) coronary artery.[16] SVG stenosis also can be treated with stenting; however, stenting usually is limited to grafts with focal or discrete disease. Outcomes are much poorer for diffusely degenerated SVGs. The risk of embolization from SVG atherosclerosis to the distal coronary bed is also greater compared with intracoronary or arterial graft stenting. Recent advances in percutaneous techniques include catheter-based systems designed to capture atheromatous debris. These advances are believed to decrease procedural morbidity and long-term graft restenosis rates. However, further studies are necessary to compare the long-term outcomes of these newer techniques with the outcomes from operative revascularization.

## SURGICAL THERAPY

The increased complexity of redo-CABG surgery is due to various unique anatomic considerations including the risks of sternal reentry, potential injury to stenotic or patent bypass grafts, difficulty with cannulation of the reoperative aorta, an increased risk of embolic phenomena, and a limitation of remaining bypass conduits (Table 29-2). The significant amount of sternal adhesions often encountered during sternal reentry increases the risk of hemorrhage as well as injury to underlying structures. Native structures that are often adherent to the posterior sternum can include the right ventricle, right atrium, aorta, innominate vein, and lung. In addition, functioning venous and arterial bypass conduits from the initial operation can be placed at risk. If difficulty with the sternotomy is anticipated, preparations for peripheral CPB should be instituted. Harvesting and preparation of the new venous and arterial conduits should be undertaken before resternotomy. Arterial cannulation for peripheral CPB can be performed through the femoral artery, or it can be performed through the axillary artery if the patient has significant aorto-iliac disease. The femoral vein is used most commonly for venous cannulation.

The use of a sagittal oscillating saw is often considered the safest approach during resternotomy (Fig. 29-3A). Sternal wires should be cut anteriorly but left in place. The oscillating saw then is used to divide the outer table of the sternum, using the wires as a guide for the depth of the cut. In this way, the intact wires posterior to the sternum provide added protection to underlying structures during sternal reentry but are removed as the inner table is divided. The inner table is divided with Mayo scissors (Fig. 29-3B). After the sternum has been opened, meticulous dissection must be employed to

**TABLE 29-2: Technical Challenges of Redo-CABG Surgery**

| |
|---|
| Sternal reentry |
| Potential injury to patent grafts |
| Cannulation of atherosclerotic aorta |
| Embolization from atheromatous saphenous vein grafts |
| Bypass conduit availability |

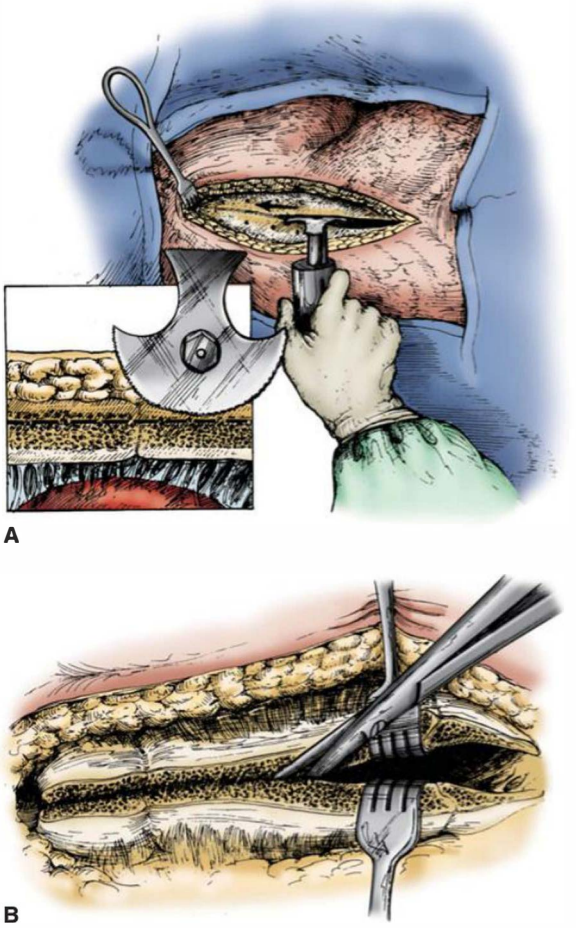



**FIGURE 29-3** **A.** Use of the oscillating saw to divide the outer table. **B.** Use of the straight Mayo scissors to divide the inner table.

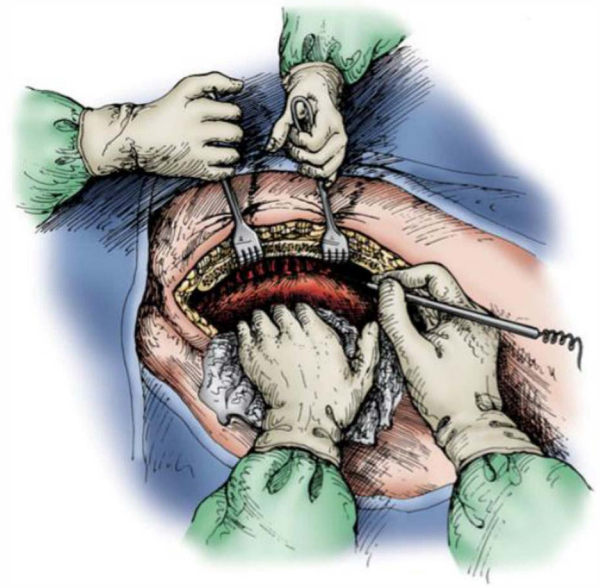


**FIGURE 29-4** Use of the electrocautery unit to separate adhesions from the sternum and chest wall.

separate adherent mediastinal structures from the chest wall (Fig. 29-4). Care must be taken to avoid excessive manipulation of venous bypass grafts because this can lead to the dissemination of atheromatous emboli. Intrapericardial dissection then continues in preparation for cannulation. Once the aorta is dissected out, it must be examined for the presence of significant atherosclerotic disease, which could lead to embolic phenomena upon cannulation. This is accomplished through palpation and epiaortic scanning to identify the most disease-free portions of the aorta. If the degree of atherosclerotic disease of the aorta is thought to be too great, the femoral or axillary arteries are other possible cannulation sites, as was mentioned above.

Myocardial protection can be provided through a combination of both antegrade and retrograde cardioplegia during redo-CABG surgery. Although antegrade cardioplegia alone may be adequate during a primary CABG, this is not the case during reoperations. Antegrade cardioplegia may be ineffective in providing protection to areas of the myocardium supplied by in situ arterial grafts and also can increase the risk of dislodging atheromatous debris from previously placed SVGs. In contrast, retrograde cardioplegia is delivered via the coronary sinus and the coronary venous system and can avoid the problems associated with antegrade cardioplegia. However, the adequacy of retrograde cardioplegia must be assessed in terms of the coronary sinus pressure, uniformity of myocardial cooling, and distention of the coronary venous system. To ensure uniform cardioplegic protection, patent in situ arterial grafts also must be occluded.

Once intrapericardial dissection of the heart is complete, the native coronary vasculature and initial bypass conduits are assessed. In conjunction with preoperative angiographic data, an operative strategy is formulated. The vessels to be bypassed and the SVGs to be replaced are determined. SVG atherosclerosis is present in a large majority of vein grafts. For this reason, replacement of all older SVGs must be considered. However, this often is not feasible because of the limitation of available bypass conduits. Unnecessary manipulation of SVGs must be avoided to prevent atheroemboli from forming. Therefore, the operative plan must be individualized, and relatively disease-free SVGs will be left in place even if they are more than 5 years old.

Many technical decisions must be made to revascularize ischemic myocardium that is being perfused by a stenotic SVG: The present SVG can be left alone or divided, and it can be replaced with a new SVG or an arterial graft. Every effort must be made to bypass left anterior descending LAD artery disease with the left IMA if this was not done at the initial operation because of the superior long-term patency rates. However, studies have shown that when new arterial grafts are used and the old vein grafts are interrupted, a hypoperfusion syndrome may develop, resulting in worsened myocardial ischemia or infarction. In addition to being a risk factor for hypoperfusion, an IMA-to-LAD graft with interruption of an old SVG was found to be an independent predictor of operative mortality.[17] This is due to an initial period of decreased flow through the arterial graft compared with the previous vein graft. The risk of hypoperfusion outweighs the risk of atheroemboli from an old SVG; therefore, old SVGs should be left in place when a new arterial graft is used to bypass the same coronary vessel. However, hypoperfusion is often not an issue when an old SVG is replaced with another SVG. Therefore, the old SVG should be interrupted in those situations.

The site of both the distal and proximal anastomoses is another challenge faced by the surgeon during redo-CABG surgery. The distal anastomotic site from the primary operation often can be reused when one is replacing an old SVG with a new one. However, progression of native vessel disease distal to this site may require the placement of a second bypass conduit on this more distal vessel. A challenge to the proximal anastomosis is posed by the often limited sites available on the reoperative aorta. This can be avoided by using sequential vein grafts that have multiple distal anastomoses but only one proximal anastomosis. In situ arterial grafts are optimal not only because they have excellent long-term patency but also because they have no proximal anastomoses. The proximal anastomosis of arterial-free grafts can be sewn to the hood of an old SVG graft, which is often free from atherosclerosis. Arterial-free grafts also can be anastomosed proximally to another arterial graft to form a composite T- or Y-type graft configuration.

## Surgical Interventions

Alternative surgical treatment strategies have become more prevalent in recent years in an effort to minimize the

potential complications associated with redo-CABG surgery. Long CPB time has been identified as an independent predictor of mortality after redo-CABG, and therefore off-pump CABG (OPCAB) has been employed as an alternative strategy for myocardial revascularization. A large, 10-year retrospective review of 296 patients undergoing redo-OPCAB demonstrated lower early mortality compared with those undergoing on-pump redo-CABG (3.3 vs 5.5 percent, $p = 0.066$).[18] The redo-OPCAB patients also had less need for prolonged ventilation or inotropic support and shorter ICU and hospital lengths of stay, as compared with conventional redo-CABG patients. However, the potential disadvantages of redo-OPCAB must also be noted. The operation becomes technically more challenging, which brings into question completeness of revascularization and graft patency. Studies have shown higher rates of incomplete revascularization in patients undergoing redo-OPCAB (17.7 vs 5.9 percent, $p < 0.01$), and showed that incomplete revascularization was an independent risk factor for cardiac death at 5 years.[19] There is an increased risk for embolization from atherosclerotic but patent vein grafts during dissection of a beating heart, and the need for the use of a partial occluding clamp on the aorta is also a disadvantage of the off-pump method. In addition, redo-OPCAB has been observed to be less effective at relieving symptoms. In one study, patients undergoing redo-OPCAB had a higher rate of angina recurrence and an increased use of nitrates at follow-up.[20] Until a large randomized-controlled trial becomes available to substantiate the benefits of redo-OPCAB, it should be used selectively after an individualized risk assessment is performed.

Sternal reentry jeopardizes structures potentially adherent to the underside of the sternum such as the aorta, right ventricle, and patent grafts that may cross the midline. A patent left IMA crossing the sternal midline can be detected on the preoperative coronary angiogram. Preoperative imaging is essential to delineate the postsurgical anatomy from the primary CABG, and peripheral cannulation with CPB may be necessary in particularly risky patients. The risks of sternal reentry can be minimized through the use of alternative incisions. If it is not necessary to revascularize multiple vascular territories of the heart, a limited thoracotomy incision can be a viable alternative to gain access to specific vessels. Anterior coronary artery revascularization can be accomplished via an anterior thoracotomy, circumflex revascularization via a lateral thoracotomy, and distal right coronary artery revascularization via an epigastric approach.[21] These limited alternative incisions can be performed in conjunction with peripheral CPB or even without CPB. Studies have shown that off-pump surgery through a thoracotomy does not increase the risk and reduces mortality and postoperative complications.[22] The proximal anastomosis or inflow vessel can be the left subclavian, the left axillary, or descending thoracic aorta, and can be accomplished with a partial occluding clamp (Fig 29-5). Since complete revascularization is usually not possible via these limited incisions, these approaches should only be considered in patients at relatively high risk with a resternotomy who require only one or two grafts.

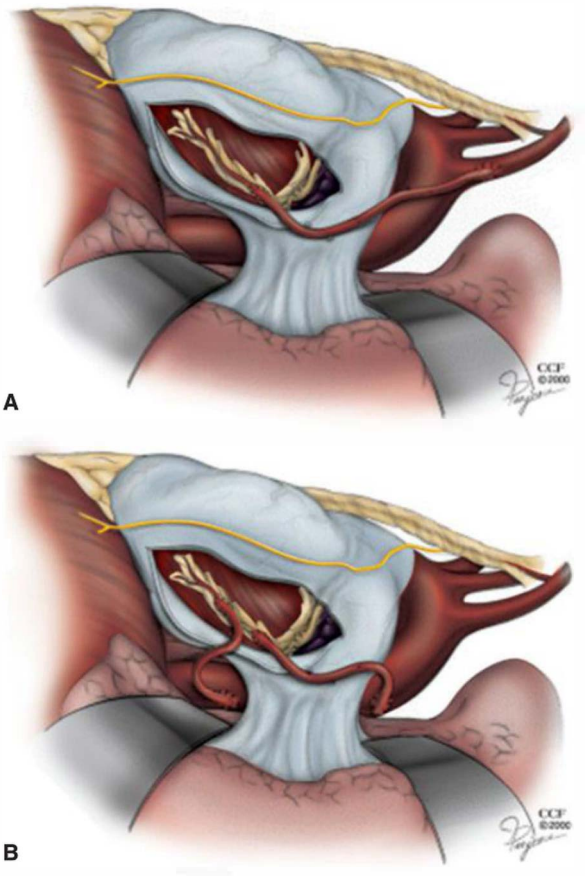



**FIGURE 29-5** **A.** View through left thoracotomy. The pericardium is opened posterior to the phrenic nerve. A previously placed vein graft to the circumflex marginal is evident. The new vein graft originates at the subclavian artery and is routed anterior to the pulmonary hilum. **B.** Same view as in A. The new vein graft originates from the descending thoracic aorta and follows a smooth course anterior to the pulmonary hilum or is routed beneath the pulmonary hilum. (Reprinted from Azoury FM, et al. Off-pump reoperative coronary artery bypass grafting by thoracotomy: Patient selection and operative technique. *Ann Thorac Surg* 2001;71(6):1959–1963. With permission from Elsevier.)

Minimally invasive direct coronary artery bypass (MIDCAB) is performed under direct vision without sternotomy or CPB. This technique is also used in reoperative patients through various incisions to revascularize one or two areas of the heart. The procedure is best suited to access anterior coronary vessels through a left anterior minithoracotomy. MIDCAB can also be combined with PCI to provide complete revascularization. Anterior coronary vessels are grafted with the left IMA if it has not been used previously. However, harvesting of the IMA is technically more difficult with the limited exposure offered by the mini-thoracotomy incision. Additional small incisions allow access to individual regions of the heart. A midline epigastric incision is made to graft posterior vessels, using the gastroepiploic

artery as the bypass conduit. Lateral coronaries can be bypassed with radial artery or SVGs via a posterior minithoracotomy. A recent study of 46 patients undergoing reoperative MIDCAB with a LIMA to the LAD on the beating heart demonstrated an in-hospital mortality of 4.7 percent with a reoperation rate of 2.3 percent.[23] Despite its limitations, studies have shown that reoperative MIDCAB can have lower rates of supraventricular arrhythmia and transfusion than traditional redo-CABG. MIDCAB also avoids the risks of resternotomy, aortic manipulation, and CPB, but does not offer an advantage for mortality, stroke, or MI. In cases in which single-territory revascularization is indicated, MIDCAB can offer a valuable treatment alternative to traditional redo-CABG.

## OUTCOMES/PROGNOSIS

### Survival

Redo-CABG is more hazardous than primary revascularization because of the increased surgical complexity as well as the vulnerable patient population undergoing reoperation. Redo-CABG patients are a substantially higher risk subgroup than patients undergoing a primary operation in terms of perioperative morbidity and mortality, relief of cardiac symptoms, and long-term survival. Overall operative mortality rates have been reported to be from 1.8 to 3.2 percent for primary CABG compared with 4.8 to 11.4 percent for redo-CABG.[1,24] Operative mortality rates are even higher for patients undergoing emergency redo-CABG, with one series citing 16.4 percent mortality.[25] The principal cause for higher operative mortality with redo-CABG is increased risk of perioperative infarction.[1] Causes of MI include incomplete revascularization as a result of distal coronary disease, vein graft thrombosis, IMA graft failure, emboli from vein grafts, injury to patent grafts, and hypoperfusion from inadequate arterial grafting (Table 29-3). Similarly, the late results for redo-CABG are less favorable than those for a primary operation. In a retrospective study of 2030 patients at Emory University, 5- and 10-year survival after reoperation were 76 and 55 percent, respectively.[25] In contrast, 56 percent of patients were alive at 15 years after primary CABG in the Coronary Artery Surgery Study (CASS) of 8221 patients.[26] In another study of 6591 primary CABG patients, 5- and 10-year actuarial survival was 90 and 75 percent, respectively. This is in contrast to the 5- and 10-year actuarial survival of 80 and 65 percent, respectively, in 508 redo-CABG patients.[27]

**TABLE 29-3: Etiology of Perioperative Myocardial Infarction**

| |
|---|
| Incomplete revascularization |
| Vein graft thrombosis |
| Internal mammary artery graft failure |
| Embolic phenomena from saphenous vein grafts |
| Injury to patent grafts |
| Hypoperfusion syndrome |

### Predictors of Mortality

In a series of 200 redo-CABG patients, only angina status and preoperative MI were identified as risk factors for operative mortality on a multivariable analysis.[28] In a separate large series of redo-CABG patients, low ejection fraction, increased age, female gender, history of arrhythmia, emergency operation, and the development of postoperative complications were all associated with increased risk of perioperative mortality.[24] Risk factors correlating with reduced long-term survival after redo-CABG surgery are older age, impaired LV function, hypertension, diabetes, congestive heart failure, emergency surgery, and female sex.[25] Despite advances in technical strategies, large national registry data suggest redo-CABG remains an independent risk factor for operative mortality.[1]

The time interval that has elapsed between the primary operation and redo-CABG impacts operative risk and mortality. Very early reoperation (1 year or less) can be correlated with a much higher mortality rate than later reoperation. Studies demonstrate mortality rates as high as 21 percent in patients after very early reoperation versus 8 percent in those reoperated on greater than 1 year after the initial operation.[29] However, as the time interval extends beyond 10 years, increased mortality rates have been observed. In one study, patients with a reoperative interval of 1 to 10 years had a 6.0 percent mortality rate, compared with 17.6 percent for those patients in whom the interval between operations was greater than 10 years.[27]

### Multiple Reoperations

Some patients require additional redo coronary revascularization procedures; however, this patient population represents a small fraction of all redo-CABG patients. In one large series, only 1 percent of all redo-CABG procedures were third- or fourth-time CABG operations.[21] Disease complexity and the risk of the operation increase with each subsequent redo-CABG. In addition, the availability of potential bypass conduits may become a limiting factor. The indications for additional operative revascularization remain the same as for first-time redo-CABG, and patients often present with disabling angina unresponsive to medical therapy. As expected, perioperative mortality and MI rates in these patients are higher than they are in first-time redo patients. The largest study to date of 150 third-time CABG patients cited an in-hospital mortality of 12 percent, and a nonfatal perioperative MI rate of 5 percent. Actuarial survival of these patients at 5 years was 76 percent.[30] More recent data show that the in-hospital mortality has improved to approximately 6.5 percent.[21] Consistent predictors of increased mortality in the patients after a third operation include age greater than

65 years and LV dysfunction with an ejection fraction less than 40 percent.[30] Despite the increased perioperative risks involved, these patients have reasonable long-term survival and symptomatic improvement after multiple redo-CABG procedures. In more recent years, some of these patients have lesions that are amenable to angioplasty and stent placement.

## SUMMARY

Redo-CABG remains a viable alternative for a number of patients, especially as the interval from the initial procedure lengthens. The treatment modalities available to patients experiencing recurring symptoms of ischemic heart disease also continue to increase in number. In addition to improvements in surgical technique, the cardiac surgeon must remain familiar with advances in percutaneous catheter interventions to devise the most appropriate treatment strategy for each patient. The differences between primary and reoperative procedures cannot be underestimated, and the surgeon must recognize the unique challenges involved. Preoperative assessment and critical analysis of each patient's anatomy are of paramount importance. With an awareness of the technical complexities and risk profile of the patients, redo-CABG can be performed with relatively low morbidity and mortality, and good long-term relief of symptoms. As operative technique and surgical technology continue to evolve, the outlook for patients who need repeat coronary revascularizations remains promising.

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## REOPERATIVE CORONARY ARTERY BYPASS SURGERY BOARD REVIEW QUESTIONS (CHAPTER 29)

1. Which of the following has not been identified as an independent risk factor for recurrent angina after coronary artery bypass grafting?

   A. Previous myocardial infarction
   B. Use of only vein grafts
   C. Incomplete revascularization
   D. Diabetes
   E. Female gender

2. Which of the following is a predictor of reoperative coronary artery bypass grafting?

   A. Older age at initial operation
   B. Male gender
   C. Use of internal mammary artery graft
   D. Single vessel disease
   E. Preserved functional status

3. The most common cause of operative mortality in patients undergoing reoperative CAB surgery is:

   A. Myocardial infarction
   B. Refractory dysrhythmias
   C. Perioperative hemorrhage
   D. Sternal dehiscence
   E. Stroke

4. When a new arterial graft is being placed on a vessel which has previously been bypassed with a vein graft, the old vein grafts should be:

   A. Ligated
   B. Ligated and divided
   C. Left in place
   D. Opened for endarterectomy
   E. Completely excised

5. Which of the following diagnostic tests is not used to assess myocardial viability prior to reoperative coronary artery bypass?

   A. Nuclear stress testing
   B. Magnetic resonance imaging
   C. Dobutamine echocardiography
   D. Coronary angiography
   E. Cardiac PET scanning

## ANSWERS

1. **Answer: D.** Diabetes has not been shown on multivariate analysis to be an independent predictor of recurrent angina after CAB. Factors that have been shown to be associated with recurrent angina include preoperative angina, use of only veins grafts, previous myocardial infarction, incomplete revascularization, female gender, smoking, and younger age at initial operation.
2. **Answer: B.** Male gender has been associated with an increased risk for reoperative CAB. Other predictors of redo-CAB include young age at initial operation, worse symptom severity, absence of an IMA graft, incomplete revascularization, impaired functional status, and multivessel disease.
3. **Answer: A.** The principal cause of mortality after reoperative CAB is myocardial infarction. This can be due to incomplete revascularization, vein graft thrombosis, IMA graft failure, embolism from atheromatous old vein grafts, injury to patent existing grafts, and hypoperfusion from inadequate arterial grafting.
4. **Answer: C.** Old vein grafts should simply be left in place. Excessive manipulation can result in embolization of atheromatous debris.
5. **Answer: D.** Coronary angiography provides anatomic details about the degree of coronary insufficiency but does not give information about viability. Nuclear stress testing and dobutamine stress echocardiography are important for establishing myocardial viability. Cardiac MRI and PET scanning are newer modalities that provide high levels of detail about myocardial function and viability.

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# Management of Concomitant Carotid and Coronary Artery Disease

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## KEY CONCEPTS

- Epidemiology
  - Stroke is a major complication of cardiac surgery, with an incidence ranging from 2.1 to 5.2 percent. As many as 22 percent of coronary artery bypass graft (CABG) candidates have hemodynamically significant carotid disease, which is a risk factor for perioperative stroke. This percentage is likely to increase as the population continues to age and CABG is used in increasingly older patients. Although carotid disease is associated with an increase in perioperative stroke risk, it is responsible for only a minority of strokes associated with CABG. In addition, it is important to note that carotid stenosis has never been shown to be an independent risk factor for perioperative stroke while controlling for aortic arch atherosclerosis.
- Pathophysiology
  - Several mechanisms have been proposed for perioperative strokes after CABG; the most important are arterial emboli and cerebral hypoperfusion. It is theoretically possible for carotid lesions to act through either mechanism, showering emboli through plaque rupture or causing hypoperfusion via thrombosis and/or obstruction of arterial flow. However, the perioperative stroke risk associated with carotid stenosis may also be related to emboli originating from aortic arch atheromas.
- Diagnostics
  - On physical examination, the most important finding is the presence of a carotid bruit. Although a carotid bruit is not pathognomonic for carotid stenosis, studies at the Johns Hopkins Hospital suggest a 40-percent positive predictive value for carotid stenosis (in excess of 70 percent) in CABG populations. From a demographic perspective, increased age, cerebrovascular disease (CVD), and peripheral vascular disease also greatly increase the likelihood of carotid disease. For patients at risk for carotid disease, duplex ultrasound represents a noninvasive means of assessing carotid disease quantitatively. Magnetic resonance angiography, cerebral angiography, and computed tomography (CT)–angiography represent more costly and/or invasive methods of assessing the degree of stenosis that may be useful in confirming duplex findings and in instances in which duplex results are indeterminate.
- Treatment
  - Treatment of patients with combined coronary and carotid disease centers on medical management with antiplatelet therapy and/or cholesterol-lowering agents and carotid endarterectomy (CEA). Patients who are candidates for CABG and in whom CEA also is indicated can be approached with one of three strategies: "staged" but separate procedures with CEA performed before CABG, the "combined" procedure with CEA and CABG performed under the same anesthesia, and "reverse-staged" procedures with CABG performed before CEA. In their practice, the authors advocate treating the symptomatic territory (i.e., carotid or coronary) first and reserving combined procedures for patients with severe symptoms in both territories. Percutaneous carotid angioplasty with or without stenting is an emerging technique that is being applied in concert with CABG in a similar fashion at select centers.
- Outcomes
  - In the absence of large prospective randomized trials, there is no high-grade evidence to support the

contention that CEA lowers perioperative stroke risk in the context of CABG. However, the most recent meta-analyses indicate that myocardial infarction (MI) is more common in patients undergoing the staged procedure and stroke rates are higher in those undergoing the reverse-staged procedure. The risk of stroke and MI is similar for the combined procedure, although overall mortality is higher than for either the staged or reverse-staged procedures. However, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS) have provided strong evidence that CEA reduces long-term stroke risk in symptomatic patients with stenosis greater than 50 percent and asymptomatic patients with stenosis greater than 60 percent. Generally, the tighter the carotid stenosis, the greater the benefit from CEA on long-term stroke risk.

- Screening
  - Many centers now screen all or a majority of CABG patients for carotid disease despite strong evidence suggesting that most perioperative strokes are caused by unrelated mechanisms. Mandatory screening is difficult to justify in the current fiscal environment given its associated costs and the lack of any proven benefit of mandatory screening over selective screening. Based on research at the Johns Hopkins Hospital, the authors advocate screening only patients who are over age 65, have a carotid bruit, or have physical symptoms of CVD [i.e., transient ischemic attack (TIA) or stroke].

## INTRODUCTION

The relationship between atherosclerotic coronary artery and carotid disease is an intuitive association well supported by clinical data. These two regions of the vasculature are closely approximated and share important similarities in structure and embryological origin. Within a given individual, these vascular beds share a common genetic background and are subject to virtually the same environment throughout the individual's lifetime. It is therefore no surprise that the finding of coronary artery disease virtually assures that there is some degree of carotid pathology and vice versa. From the standpoint of the cardiothoracic surgeon, this means that up to 22 percent of candidates for coronary artery bypass surgery will have significant carotid disease.[1] This number is likely to increase as the population continues to age and coronary artery bypass grafting (CABG) is extended to more elderly patients.

Although the importance of combined coronary and carotid disease is straightforward, its treatment is complex and controversial. Historically, the procedures to address each condition were developed separately and have been evaluated using different metrics. Traditionally, the clinical benefits of CABG were measured as reductions in the rates of myocardial infarction (MI), reintervention, and mortality rates whereas those of carotid endarterectomy (CEA) have been measured as reductions in stroke and mortality. Each procedure is associated with complications that the other is intended to prevent; MI and stroke are well-recognized complications of both CEA and CABG, respectively. Furthermore, one must consider that although carotid disease is often present in coronary bypass patients, the majority of these patients experience no symptoms from their cerebrovascular disease (CVD). In deciding which procedure(s) is appropriate for each subpopulation, one must bear in mind its impact on all endpoints (e.g., MI, stroke, death) weighed against the likelihood of all complications. Lastly, less invasive procedures such as "off-pump" CABG and carotid stenting have become more widespread in recent years, adding a further layer of complexity to surgical treatment options. This chapter guides cardiothoracic surgeons through the challenges of identifying and managing carotid disease in coronary bypass patients and reviews the evidence for and against current treatment options.

## CAROTID DISEASE AND PERIOPERATIVE STROKE ASSOCIATED WITH CORONARY ARTERY BYPASS SURGERY

Stroke is one of the most prevalent and debilitating complications of coronary artery bypass surgery and one that frequently negates the benefits of coronary revascularization. Clinically speaking, perioperative stroke is defined as an acute neurologic event secondary to circulatory impairment lasting more than 24 hours and occurring within a specified period of time following surgery. Nearly all centers define stroke in this manner and most obtain radiologic imaging [i.e., computed tomography (CT) or magnetic resonance imaging (MRI)] to delineate the distribution and extent of cerebral injury after a perioperative stroke. Although there is variability in the definition of perioperative stroke (e.g., 14 vs 28 days), most strokes present within the first 3 days after coronary bypass surgery. Over the past 2 decades, the incidence of perioperative stroke in the general CABG population has remained fairly constant, ranging from 2.1 to 5.2 percent.[2,3] A variety of risk factors have been identified for perioperative stroke in CABG patients (Table 30-1) and several closely related mechanisms have been proposed (Table 30-2), the most important of which are arterial emboli and cerebral hypoperfusion. It is theoretically possible for carotid lesions to affect strokes by either of these mechanisms in the postoperative period, incurring emboli though plaque rupture,

**TABLE 30-1: Risk Factors for Perioperative Stroke in Coronary Bypass Patients**

| Demographic | Preoperative | Intraoperative |
|---|---|---|
| Age >65 retired | Hypertension | Cardiopulmonary bypass time |
| | Diabetes mellitus | Use of intra-aortic balloon pump |
| | Carotid bruit | Mean cross-clamp time |
| | Prior CVA | |
| | Prior CVD (CVA or TIA) | Use of membrane oxygenator |
| | Left main disease >50 | |
| | Tobacco use >10 pack-years | |

CVA, cerebrovascular accident; CVD, cerebrovascular disease; TIA, transient ischemic attack.

thrombosis, or diminished arterial flow. However, since the carotid arteries are not surgically manipulated during CABG and carotid thrombi are rarely seen on imaging, it has been postulated that carotid stenosis and/or occlusion cause strokes primarily via cerebral hypoperfusion during low cardiac output states (e.g., while on cardiopulmonary bypass or in the early postoperative period).

In a large meta-analysis, Naylor et al. concluded that less than half of CABG patients who suffered perioperative strokes had significant carotid disease, defined as either significant stenosis or occlusion.[4] Naylor et al. also demonstrated that the degree of carotid disease was statistically associated with increasingly high rates of perioperative stroke in CABG patients, which ranged from 3 percent in patients with mild disease up to 7 to 11 percent in patients with carotid occlusion. An extensive retrospective study from our practice at The Johns Hopkins Hospital yielded similar results.[5] However, carotid disease is a fairly specific risk factor for aortic arch atherosclerosis,[6] which is widely believed to be the most important source of arterial emboli in CABG-related strokes. As a result, although the finding of carotid disease clearly increases the risk of perioperative stroke in CABG, it remains unclear whether the link between carotid disease and perioperative stroke is truly causal, since carotid disease alone has never been proven to be an independent risk factor for perioperative stroke while controlling for aortic atherosclerosis. At the same time, there are reports of individuals in whom the finding of preoperative stenosis preceded a "watershed" stroke in the distribution of a stenotic carotid artery.[7] In summary, carotid disease is associated with an increased stroke risk in CABG patients, but less than half of CABG-related strokes occur in patients with carotid disease and it is likely that only a subset of these strokes are due to carotid stenosis per se rather than related conditions.

Although the effect of carotid disease on perioperative stroke risk in CABG remains uncertain, its effect on long-term stroke risk is well documented. Carotid disease is thought to cause between 20 and 30 percent of strokes.[8] With regard to long-term stroke risk, the natural history of carotid disease in CABG patients is presumably similar to that of nonsurgical patients in large prospective studies of carotid stenosis, such as the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and Asymptomatic Carotid Atherosclerosis Study (ACAS).[9,10] No large, prospective, controlled trials to date have specifically addressed the impact of carotid stenosis and/or occlusion or their related therapies on the long-term rates of stroke free survival in CABG patients. A final point to consider is that there is likely a small degree of mechanistic overlap between "long-term" and "perioperative" strokes; there are bound to be CABG patients with carotid stenosis who, by chance, suffer strokes due to carotid plaque rupture unrelated to the operation itself, within the perioperative period.

**TABLE 30-2: Mechanisms of Perioperative Stroke in Coronary Bypass Patients**

| Mechanism of Stroke | % of Perioperative Strokes in Coronary Artery Bypass |
|---|---|
| Embolic | 62.1 |
| Unclassified | 13.9 |
| Multiple etiologies | 10.1 |
| Hypoperfusion | 8.1 |
| Lacunar | 1 |
| Thrombotic | 1 |

Data from Likosky DS, et al. Determination of etiologic mechanisms of strokes secondary to coronary artery bypass graft surgery. *Stroke* 2003;34:2830.

## CORONARY ARTERY DISEASE AND MYOCARDIAL INFARCTION ASSOCIATED WITH CAROTID ENDARTERECTOMY

It has long been known that vascular lesions outside the coronary vascular bed can be "index lesions" of MI. Indeed, MI is a well-documented complication of several commonly performed peripheral vascular interventions, such as aortic or infrainguinal procedures. The mechanism is thought to be embolic, as fragments of plaque from the diseased vascular bed are mobilized during surgical manipulation and become lodged in already-stenosed coronary arteries. Nonfatal and fatal MIs remain devastating postoperative complications of CEA, although the incidence of MI in ACAS was less than 1 percent.[11] These numbers seem surprisingly low when one considers that up to 50 percent of patients with carotid disease have some degree of coronary artery disease. Of course, MI rates are likely to be somewhat higher in CABG patients who, by definition, have severe coronary artery disease.

## CAROTID DISEASE IN CORONARY ARTERY BYPASS PATIENTS

Previous studies have reported an incidence of carotid disease in CABG patients ranging from 2 to 22 percent.[5] This range is rather wide because the definition of "significant" carotid disease varies between centers. For example, even ACAS and NASCET stratified their respective cohorts using different numerical thresholds. Specifically, ACAS defined 60 percent luminal stenosis as significant whereas NASCET initially employed a 70-percent threshold that was later changed to 50 percent.[9,10] After ACAS showed a significant but underwhelming clinical benefit for CEA using the 60 percent threshold, numerous follow-up studies have used greater degrees of carotid stenosis as thresholds to trigger surgical intervention. The ambiguity of the term "significant stenosis" is equally apparent in studies of carotid disease in CABG populations, where thresholds have routinely ranged from 50 to 80 percent luminal narrowing.

Regardless of the threshold one chooses to define significant carotid disease, there are several ways to identify and quantify carotid lesions. Ideally, the process begins by including questions in the history designed to identify patients at high risk for carotid disease. Because the etiologies of carotid and coronary artery disease are so similar, it is best to focus on the risk factors that have been validated in previous studies of carotid disease within CABG populations (Table 30-3). On physical examination, the most important finding is the presence of a carotid bruit. Although a carotid bruit is not pathognomonic for carotid stenosis, at our center nearly 40 percent of CABG patients with a bruit had carotid stenosis in excess of 70 percent as measured by carotid duplex ultrasound.[5] In addition, any exam findings indicative of CVD (e.g., focal neurologic deficits) or peripheral vascular disease (e.g., weak distal extremity pulses, popliteal bruits) also greatly increase the likelihood of carotid disease.

For those patients identified as high risk for carotid disease, screening by duplex ultrasound represents a noninvasive means of quantitatively assessing carotid disease. Duplex ultrasonographic measurements are obtained from peak blood flow velocities measured across the proximal internal carotid artery, which are correlated to the gold standard of percentage luminal occlusion derived from digital subtraction angiography. For example, at our institution we use the criteria derived by Grant et al.[12] to translate duplex measurements to percentage luminal stenosis. Equivocal cases are then further evaluated by magnetic resonance angiography and/or CT angiography. With angiography, we define percentage stenosis according to the NASCET criteria: $100 \times (1-S/D)$, where $S$ = diameter at the point of greatest luminal narrowing due to stenosis and $D$ = the luminal diameter in the "normal" portion of the carotid at a point at which the walls are parallel.

It is important to note that different measurement criteria have been used in the past. The European Carotid Surgery Trial used an estimate of the unseen carotid bulb wall in place of $S$.[13] Still another "common carotid method" uses the diameter of the common carotid in place of $S$. Although there are advantages and disadvantages with each method, what matters most is consistency.

**TABLE 30-3: Risk Factors for Carotid Disease in Coronary Bypass Patients**

| Highly Significant ($p$ <0.01) | Significant ($p$ <0.05) |
|---|---|
| Prior CVA | Tobacco use[a] |
| Prior CVD (CVA or TIA)[a] | Left main disease >50 |
| Carotid bruit[a] | Hypertension[a] |
| Peripheral vascular disease | Prior CEA |
| Age >65[a] | |

CVA, cerebrovascular accident; CVD, cerebrovascular disease; TIA, transient ischemic attack.

[a]Shared risk factors for stroke and cerebrovascular disease in coronary artery bypass patients.

## CAROTID INTERVENTION

When a patient is diagnosed with carotid stenosis (i.e., nonocclusive carotid disease), two treatment strategies are available: (1) medical management with antiplatelet therapy and/or cholesterol-lowering agents and (2) CEA or percutaneous angioplasty with or without carotid stenting. The choice of therapy is typically guided by the presence or absence of cerebrovascular symptoms (i.e., prior stroke or transient ischemic attack) and the extent of stenosis based on the results of several large multicenter prospective randomized clinical trials conducted in the 1980s and 1990s.

### Carotid Endarterectomy

NASCET compared CEA to medical management with aspirin and identified a 15 percent absolute reduction in stroke risk (i.e., 25 vs 10 percent) at 2 years in symptomatic patients with carotid stenosis in excess of 70 percent.[9] Further analysis showed a more modest benefit in patients with carotid stenosis in excess of 50 percent.[14] Of the three largest studies on asymptomatic cohorts, the CASANOVA and VA trials found no significant benefit for CEA.[15,16] ACAS identified an absolute stroke risk reduction of just 5 percent (i.e., 10–15 percent).[10] Since the degree of benefit patients receive from CEA is directly proportional to their preoperative stroke risk, many authors have sought to incorporate a variety of risk factors in addition to the degree of carotid stenosis in order to expand indications for CEA to all patients likely to benefit from surgery. Critics of ACAS and NASCET maintain that CEA is now less effective because medical therapies have evolved while the majority of CEAs are now performed by surgeons with higher complication rates than those at the centers of excellence used in the landmark studies. The net result is that CEA is strongly indicated in symptomatic patients with carotid stenosis in excess of 70 percent. The

role of CEA is more controversial in asymptomatic patients with carotid stenosis, but is generally recommended in cases of severe or critical (e.g., 80 percent) carotid disease. It is unknown how these results extrapolate to CABG patients, in whom operative complications such as MI and/or death are likely to be much higher and may even negate the stroke-risk benefits of CEA.

### Carotid Stenting

The past 2 decades have seen a rapid expansion in endovascular intervention for carotid disease. A recent meta-analysis performed by Meier et al. included all published trials comparing stenting to CEA published between January 1990 and July 2009 and found CEA to have better short-term outcomes than CAS, with a significantly higher risk of periprocedural stroke in the CAS group.[17] However, there was no significant difference in intermediate-term outcomes between the two groups, and the CAS group actually had a lower rate of cranial nerve injuries and MIs. Recent data from the large multicenter Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) yielded similar results, demonstrating a higher risk of stroke during the periprocedural period with stenting and a higher risk of MI with endarterectomy.[18] Overall, however, there was no significant difference in the risk of composite primary outcome of stroke, MI or death between the group undergoing CEA and the group undergoing stenting. Long-term outcomes for stenting are also promising, with the results from the randomized trial, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE), demonstrating a lower rate of carotid revascularization procedures after 1 year in patients receiving stents compared with those who underwent endarterectomy.[19]

In general, recent studies have used the indications for carotid stenting that were based upon the original NASCET and ECST criteria for endarterectomy. As new data emerge comparing carotid stenting to CEA, the threshold for intervention according to risk–benefit analysis will continue to evolve. As was originally seen with the NASCET data, the risks of CEA greatly depended on the skill and experience level of the surgeon; clearly, the same holds true in attempting to calculate the risks of intervention with stenting procedures. The substantial heterogeneity between studies and the various levels of operator skill and experience have made it difficult to compare carotid stenting with CEA. Toward this end, recent emerging data from large multicenter trials, such as the CREST Trial, will provide further guidance and work to change current management algorithms.

## SURGICAL AND INTERVENTIONAL TREATMENT OF COMBINED CORONARY AND CAROTID DISEASE

Surgical treatment for concomitant coronary and carotid disease varies between centers, primarily because there are no large multicenter prospective randomized trials to guide therapy. Consequently, guidance must be pieced together using a combination of data from small studies, meta-analyses and local institutional experience. In our practice, we advocate treating the symptomatic territory (i.e., carotid or coronary) first and reserving combined procedures for those with symptoms in both territories. The reasoning for our recommendation is summarized later. A well performed series of meta-analyses[20–22] of virtually all prior reports published by Naylor et al. has helped inform the practice in recent years.

### Staged Carotid Endarterectomy–Coronary Artery Bypass Grafting

In the staged approach, the carotid lesion is addressed first by CEA, followed by CABG at a later point. The time interval between the procedures has varied in the literature from days to months. The rationale behind this sequence is predicated on a reduction in perioperative stroke risk due to a prophylactic treatment of the carotid lesion. This strategy is most appropriate in patients whose carotid disease is equally or more advanced than their coronary disease, as they must forego CABG for some period of time. Conversely, this strategy is inappropriate for patients with critical coronary stenosis or severe multiple-vessel disease, since the heightened risk of perioperative MI remains unaddressed. Naylor's data[22] on combined procedures to date have shown that perioperative MI is slightly more common than perioperative stroke in patients undergoing staged CAE–CABG (Table 30-4).

**TABLE 30-4: Complication Rates for Patients Undergoing Combined Procedures**

| | Stroke | MI | Stroke/MI/Death |
|---|---|---|---|
| Synchronous CEA/CABG | 4.6 (3.9–5.4) | 3.6 (3.0–4.2) | 11.5 (10.1–12.9) |
| CEA + "Off-pump" CABG | NA | NA | 3.5 (1.6–5.5) |
| CEA–CABG (staged) | 2.7 (1.6–3.9) | 6.5 (3.2–9.7) | 10.2 (7.4–13.1) |
| CABG–CEA (reverse-staged) | 6.3 (1.0–11.7) | 0.9 (0.5–1.4) | 5.0 (0.0–10.6) |
| CAS–CABG | 4.2 (2.4–6.1) | 1.8 (0.5–3.0) | 9.4 (7.0–11.8) |

Data compiled from references 20–22.
Complication rates expressed in percentages.
95% confidence intervals in parentheses.

## Reversed-Staged Coronary Artery Bypass Grafting–Carotid Endarterectomy

In patients whose coronary disease is more critical than their carotid disease, a reversed-staged approach may be appropriate. MI was the most common complication associated with CEA in the ACAS study, and has been shown to occur with greater frequency in patients with unstable angina and coronary artery disease. Patients who have recently undergone CABG have reduced their risk of perioperative MI and are thus thought to be better candidates for subsequent CEA. As one would expect, the results of the reversed-staged approach run are essentially the opposite of those of the staged approach (Table 30-4), with higher rates of stroke than MI.

## Combined Carotid Endarterectomy–Coronary Artery Bypass Grafting

For patients experiencing symptoms of both coronary and carotid diseases, it may be advantageous to operate on both territories simultaneously. Because the prospect of addressing both lesions and their associated complications is so appealing, there have been a disproportionate number of papers studying this combined approach. Various techniques have been demonstrated: (1) CEA prior to opening the thorax, (2) CEA after opening the thorax but prior to cannulation, and (3) CEA while on cardiopulmonary bypass. The first is by far the most popular.

The results of the combined approach have varied widely. In the meta-analyses conducted to date, the incidence of stroke, MI, and death have each been around 5 percent.[22–25] These numbers are likely skewed by the fact that combined procedures are more likely to be offered to sicker patients. At the same time, there are indications that the technical complexity of operating on both territories has poor reproducibility and may even be dangerous when attempted outside centers of excellence. For example, a study of 226 patients treated with concomitant procedures at community-based hospitals demonstrated a combined stroke/mortality rate of 17.7 percent.[26]

## Staged Carotid Artery Stenting–Coronary Artery Bypass Grafting

As published data on CAS have become more positive over the past decade, there have been an increasing number of reports in which CAS has been used in place of CEA in the traditional staged strategy prior to CABG. Naylor's recent meta-analysis of this (admittedly heterogeneous) data revealed comparable rates of perioperative complications as compared with other more traditional forms of combined procedures described earlier, though data on MI were not reported. Given that CAS is less invasive than CEA, this can be seen as a motivation for expanding indications for CAS–CABG in favor of CEA–CABG. One potential complicating factor when considering combining CAS and CABG procedures is the need to balance the benefits of pre- and postprocedural antiplatelet therapy with regard to stent patency against the risk of perioperative hemorrhage related to CABG. However, Naylor et al.[21] report that although data on bleeding complications are available for only a subset of patients who have undergone CAS–CABG, there were apparently only seven instances of major perioperative hemorrhage (0.9 percent), only two of which were fatal (0.3 percent).

## Carotid Endarterectomy—Off-Pump Coronary Artery Bypass Graft

"Off-pump" CABG refers to the technique of performing coronary artery bypass without aortic cross-clamping. Although there is relatively little data on combined CEA and off-pump CABG, preliminary results suggest that this approach is associated with lower rates of perioperative complications than either traditional approaches or those employing CAS (Table 30-4).[20] One possible explanation for this result is that, as stated earlier, the association between carotid stenosis and perioperative stroke in CABG may be an indirect relationship mediated by aortic arch disease. If that is in fact the case, then the low rates of complication in these series may be due to the lack of aortic cross-clamping rather than CEA itself.

# RISK-STRATIFICATION MODELS FOR PREOPERATIVE CAROTID SCREENING PRIOR TO CORONARY ARTERY BYPASS GRAFT

Based on the issues already discussed, carotid intervention (i.e., CEA or stenting) is indicated in only about 5 percent of the total CABG population. Screening all CABG patients for carotid disease with duplex ultrasonography requires significant economic resources, inconvenience to patients, and potential delay to CABG. An alternative approach is to use a selective screening approach based on identified risk factors for carotid disease. At our institution, we selectively screen patients at "high risk" for both carotid disease and stroke: patients with cerebrovascular symptoms, a carotid bruit or age in excess of 65 years. Our algorithm (Fig. 30-1) has a sensitivity in excess of 80 percent and specificity of 40 percent in identifying significant operable carotid disease (>70 percent stenosis), and has reduced screening loads by 40 percent.[5] Furthermore, a post hoc retrospective analysis indicates that all CABG patients evaluated at our center over a 2-year period that were found to have significant carotid disease and suffered perioperative strokes would have been

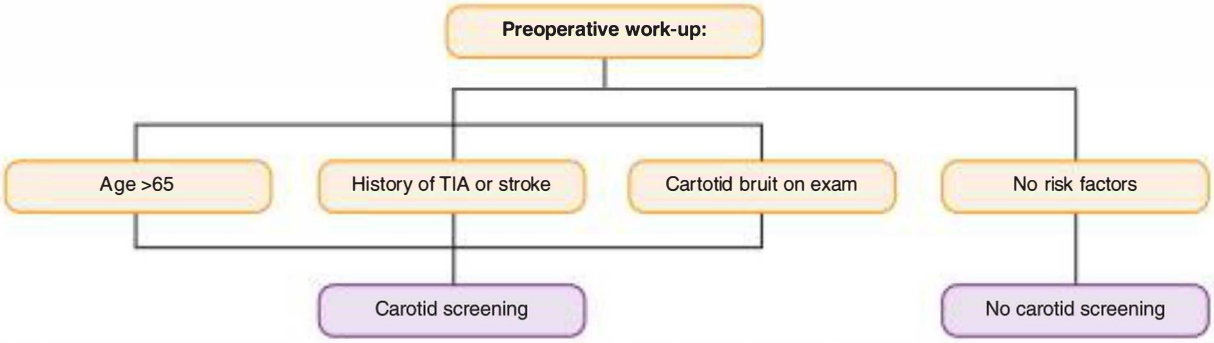



**FIGURE 30-1** Preoperative carotid duplex screening algorithm in use at Johns Hopkins Hospital. (Durand DJ, Perler BA, Roseborough GS, et al. Mandatory versus selective preoperative carotid screening: A retrospective analysis. *Ann Thorac Surg* 2004;78:159–166.)

identified as "high risk" for carotid stenosis according to our selective screening criteria. The incidence of asymptomatic carotid disease in "low-risk" patients that would have gone unscreened was only 5 percent and CEA would only have been indicated in 1 percent of these patients. We advocate this screening algorithm, or one that incorporates additional stroke risk factors (e.g., peripheral vascular disease), to optimize preoperative carotid screening.

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## MANAGEMENT OF CONCOMITANT CAROTID AND CORONARY ARTERY DISEASE BOARD REVIEW QUESTIONS (CHAPTER 30)

1. Which of the following is correct regarding perioperative stroke?
   A. More than half of CABG patients suffering perioperative stroke will have significant carotid artery disease.
   B. Carotid occlusion is associated with a stroke incidence of 3 percent after CABG.
   C. The degree of carotid disease is not associated with risk of stroke.
   D. Carotid disease is a risk factor for aortic arch atherosclerosis.
   E. The finding of carotid disease does not increase the risk of stroke.

2. Which procedure has the lowest incidence of stroke?
   A. Synchronous CEA–CABG
   B. CEA, then CABG
   C. CABG, then CEA
   D. CAS–CABG

3. Which procedure has the lowest incidence of myocardial infarction?
   A. Synchronous CEA–CABG
   B. CEA, then CABG
   C. CABG, then CEA
   D. CAS–CABG

4. Which is true regarding outcomes of trials for carotid endarterectomy?
   A. NASCET identified a 15 percent absolute reduction in risk of stroke
   B. CASANOVA demonstrated a stroke risk reduction of 10 percent after CEA
   C. The VA trials showed a stroke risk reduction of 8 percent
   D. ACAS revealed an absolute risk reduction of 20 percent

5. Which is correct regarding carotid stenting compared to CEA?
   A. There is a lower incidence of periprocedural stroke
   B. CEA has improved intermediate-term outcomes
   C. There is a lower incidence of cranial nerve injury
   D. There is a higher incidence of myocardial infarction
   E. There is a higher incidence of carotid revascularization procedures

## ANSWERS

1. **Answer: D.** Carotid disease is a fairly specific risk factor for aortic arch atherosclerosis. Less than half of CABG patients suffering perioperative stroke will have significant carotid artery disease. Carotid occlusion is associated with a stroke incidence of 7 to 11 percent after CABG. Increasing degree of carotid disease is associated with an increasing risk of stroke, and the finding of carotid disease clearly increases the risk of stroke after CABG.
2. **Answer: B.** Staged carotid endarterectomy followed by CABG has the lowest incidence of stroke at 2.7 percent. Staged carotid stenting followed by CABG has a stroke incidence of 4.2 percent, synchronous CEA–CABG has a stroke incidence of 4.6 percent, and staged CABG followed by CEA has a stroke incidence of 6.3 percent.
3. **Answer: C.** Staged CABG followed by CEA has the lowest incidence of MI at 0.9 percent. Staged carotid stenting followed by CABG has an MI incidence of 1.8 percent, synchronous CEA-CABG has an MI incidence of 3.6 percent, and staged carotid endarterectomy followed by CABG has an MI incidence of 6.5 percent.
4. **Answer: A.** The NASCET trial demonstrated an absolute risk reduction of 15 percent in patients with carotid stenosis >70 percent after CEA. Neither the CASANOVA nor the VA trials found a significant benefit for CEA in asymptomatic patients. The ACAS trial showed an absolute risk reduction of 5 percent.
5. **Answer: C.** There is a lower incidence of cranial nerve injury after carotid stenting. There is also a lower incidence of myocardial infarction and carotid revascularization procedures after carotid stenting, but a higher incidence of periprocedural stroke. In general, intermediate-term outcomes are similar between carotid stenting and CEA.

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# Mechanical Complications of Myocardial Infarction

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## KEY CONCEPTS

- Epidemiology
  - Six to ten percent of patients develop cardiogenic shock after myocardial infarction.
  - Mitral regurgitation (MR) occurs in 8 to 50 percent of patients after myocardial infarction.
  - Post-infarct ventricular septal defects (VSD) occurs in <0.5 percent of myocardial infarction (MI) patients.
  - Only 24 percent of medically treated patients with post-infarct VSD survive 30 days.
  - In autopsy series, 30 percent of myocardial infarction (MI) is accompanied by ventricular free wall rupture (VFWR).
  - The incidence of left ventricular aneurysms depends on exact definition; 10 to 35 percent of patients will develop region of systolic akinesia or dyskinesia after transmural myocardial infarction (MI).
- Pathophysiology
  - In cardiogenic shock associated with MI, worsening ventricular function leads to decreased coronary perfusion, worsening ischemia, and an enlarging infarct zone.
  - Three primary pathologic mechanisms exist for post-infarct MR:
    - Papillary muscle rupture
    - Acute ischemic MR
    - Chronic ischemic MR.
  - Post-infarct VSD follows large transmural infarction with weakening of the septal wall.
  - Post-infarct VSD results in left-to-right shunt of variable magnitude with diversion of blood flow from systemic to pulmonary circulation and low-cardiac-output state, ultimately into cardiogenic shock.
  - VFWR occurs after large, transmural MI in myocardium without collaterals.
  - Traditionally ventricular aneurysm is defined as region of myocardium exhibiting abnormal diastolic contour with systolic dyskinesia and paradoxic bulging.
  - Ventricular remodeling after large transmural infarct leads to infract expansion and aneurysm formation.
- Clinical features
  - Symptoms of systemic and coronary hypoperfusion, including cold, clammy extremities, cyanosis, oliguria, and altered sensorium.
  - Cardiogenic shock associated with MI leads to pulmonary edema, chest pain, and shortness of breath.
  - New holosystolic murmur best heard at the apex is noted in MR associated with MI.
  - Post-infarct VSD typically occurs 5 to 6 days after MI
  - Eighty percent of VFWR occur within 7 days after infarct.
  - Subacute VFWR results in a worsening pericardial effusion and hypotension without pulseless electrical activity and cardiac arrest.
  - Pseudoaneurysm formation from VFWR occurs approximately 3 months after MI with variable symptomatology.
  - Commonly presents with congestive heart failure
  - LV aneurysm commonly presents with congestive heart failure, angina, and/or dyspnea.
  - Mural thrombus present in 50 percent of ventricular aneurysm patients at surgery.
- Diagnostics
  - Invasive hemodynamic monitoring important in optimizing both coronary and systemic perfusion.
  - Electrocardiography (ECG) confirms cardiac ischemia; chest X-ray rules out pneumothorax.
  - Emergent echocardiography (ECHO) to rule out other mechanical causes of shock, including papillary muscle or ventricular rupture.

- Echocardiography (ECHO) allows evaluation of left ventricular (LV) function and mitral apparatus; can accurately diagnose pulmonary muscle (PM) rupture as well as exclude other mechanical causes of cardiovascular collapse.
- Location of infarct of echocardiography (ECHO) correlates with location of post-infarct VSD.
- ECHO is important to differentiate post-infarct VSD from acute, severe mitral regurgitation (sensitivity and specificity ~100 percent).
- Angiography allows delineation of coronary anatomy, estimation of ventricular aneurysm size, and guided placement of intra-aortic balloon pump (IABP).
- Rapid pericardiocentesis is both diagnostic and therapeutic for VFWR.
- Echocardiography (ECHO) identifies effusion with pericardial clots for VFWR; Doppler evaluation may identify rupture site.
- MRI may be useful in evaluating pseudoaneurysms.

- Treatment
  - Medical
    - No pharmacologic agent has been demonstrated to improve survival for cardiogenic shock associated with acute MI; inotropes/vasodilators/vasopressors should be used to stabilize the patient in preparation for definitive therapy.
    - Thrombolysis is of unproven benefit for patients in cardiogenic shock.
    - Medical therapy for acute MR and papillary muscle rupture is supportive only.
    - Intra-aortic balloon pump counterpulsation (IABP) improves both systemic and coronary perfusion while reducing systemic vascular resistance and left-to-right shunt in post-infarct VSD.
  - Surgical
    - IABP counterpulsation may improve hemodynamic stability in patients who undergo systemic thrombolysis; may improve outcomes in patients with cardiogenic shock; excellent option for hemodynamic stabilization.
    - Clear long-term benefit to percutaneous coronary revascularization in patients with cardiogenic shock (SHOCK trial). Successful angioplasty is associated with significant improvements in 30-day mortality.
    - Emergent CABG improves survival in most studies of cardiogenic shock; optimal indications unclear but important treatment where PCI is unsuccessful or inappropriate.
    - Left ventricular assist device (LVAD) and orthotopic heart transplantation are options when revascularization is not possible or ineffective.
    - Surgical indications for post-MI MR include
      - PM rupture
      - Acute, severe MR not improved by percutaneous coronary intervention or thrombolysis
      - Chronic 3+ to 4+ MR and symptomatic coronary disease
      - Other indications: LVESVI ≥80 mL/m², regurgitant fraction 50 percent greater than forward ejection fraction, estimated regurgitant orifice >20 mm².
    - Multiple repair techniques described for post-infarct VSD, including apical amputation, patch closure, and infarct exclusion
    - Pseudoaneurysm repair primarily by closure of neck or patch repair similar to true aneurysms.
    - Asymptomatic patients with small aneurysms can be managed medically; larger symptomatic aneurysms require operative repair.
    - Multiple ventricular aneurysm repair techniques described: plication, linear repair, variety of geometric repairs.
    - Geometric ventricular aneurysm repairs (Dor, Jatene, Cooley) have advantage of restoring LV geometry and preserving long-term LV function.
- Outcomes and prognosis
  - Hospital mortality rates in patients presenting in cardiogenic shock after acute MI are 60 percent vs 8 percent for those without cardiogenic shock; emergent revascularization improves survival in nearly all patients.
  - Operative mortality in acute severe MR (with or without PM rupture) ~20 percent.
  - Operative mortality remains high for post-infarct VSD (though better than medical therapy alone): 20 to 50 percent.
  - Hospital survivors after post-infarct VSD repair have excellent long-term survival (61 percent at 8 years).
  - Operative mortality approximately 25 percent with only patch repair of VFWR; similar operative mortality for those with pseudoaneurysms.
  - Operative mortality for ventricular aneurysm repair 2 to 13 percent; five-year survival from 20 to 42 percent.
  - Survival after ventricular aneurysm repair (short and long term) is probably lower with geometric repairs than with linear repairs.
  - Measurements of LV function improve after aneurysm repair and maintained long term.

## OVERVIEW

The first clinical description of myocardial infarction (MI) was reported by Herrick in 1912.[1] He concluded from the clinical history that "while sudden death often does occur, yet at times it is postponed for several hours or even days, and in some instances, a complete, that is functionally complete, recovery ensues." In the current era, a complete recovery after an acute MI has become the norm rather than the exception. Unfortunately however, the mortality for some patients remains devastatingly high. In particular, patients with cardiogenic shock after an acute MI have less than a 50 percent chance of surviving their hospital stay.[2,3]

Cardiogenic shock in acute MI may result from a variety of mechanical complications. Most commonly it results from ventricular infarction and dysfunction alone, but other mechanical processes may contribute to the syndrome: ventricular septal rupture (VSR), ventricular free wall rupture, and ischemic mitral regurgitation (IMR).[4] Although surgical therapies for these three conditions have long been recognized, the importance of timely revascularization in patients with cardiogenic shock in the absence of ventricular rupture or mitral regurgitation (MR) has received increased attention recently (see the decision-making flowchart; Fig. 31-1).

The topics covered in this chapter include (1) post-MI cardiogenic shock and ventricular dysfunction, (2) ischemic mitral valve (MV) disease, (3) postinfarction VSR, (4) postinfarction ventricular free wall rupture, and (5) ventricular aneurysms.

# POSTMYOCARDIAL INFARCTION, CARDIOGENIC SHOCK, AND VENTRICULAR DYSFUNCTION

## Introduction

Cardiogenic shock is a clinical syndrome that is characterized by hypotension and systemic hypoperfusion in the setting of ineffective cardiac function. Although the first report of circulatory collapse secondary to MI may have occurred as early as 1794 with Sir Everald Home's description of the life of the British surgeon Sir John Hunter, Herrick first recognized the clinical signs of cardiogenic shock: cold clammy extremities, oliguria, and an altered mental status.[5,6] These clinical signs are accompanied by alterations in hemodynamic parameters: systolic blood pressure (SBP) less than 90 mm Hg, cardiac index (CI) less than 2.2 L/min/m$^2$, and pulmonary capillary wedge pressure greater than 15 mm Hg, indicating inadequate cardiac function despite adequate preload.

## Pathophysiology

### MYOCARDIAL ISCHEMIA AND INFARCTION

With progressive atherosclerosis of the coronary arteries, normal intraluminal diameter is preserved initially through compensatory outward remodeling; however, eventually these stenoses become functionally important and coronary artery disease becomes symptomatic.[7] Plaque rupture may occur at any time, leading to intraluminal thrombosis.[8] Usually this occurs in angiographically insignificant arteries, but it may cause total occlusion of epicardial arteries, resulting in acute myocardial hypoperfusion and ischemia. Occlusion of coronary arteries for less than 15 min results in reversible myocardial injury; longer periods result in irreversible damage.[9,10] Brief periods of ischemia correspond clinically to periods of angina (stable or unstable) and may occur on a daily basis[11]; longer periods result in MI.

### STUNNED MYOCARDIUM

Within the first few minutes of ischemia, hypoxic myocytes stop contracting, resulting in regions of akinesia and dyskinesia.[11] After reperfusion (whether by relaxation of coronary artery spasm, cessation of exercise in stable angina, or pharmacologic or mechanical reperfusion), regions of viable post-ischemic myocardium may take hours to days to return to normal function; this delay has been termed myocardial stunning.[12–14] It originally was described in canine models of coronary occlusion and reperfusion and represents contractile dysfunction after *acute* ischemic injury. It includes left ventricular (LV) dysfunction after thrombolysis or angioplasty and may be involved in unusual cases of coronary spasm and severe exercise-induced ischemia. The pathogenesis of myocardial stunning is not completely understood. The primary mechanism is thought to be liberation of oxygen free radicals and myocyte adenosine triphosphate (ATP) depletion during reperfusion, but alterations in calcium homeostasis (including excitation-contraction decoupling resulting from sarcoplasmic reticulum dysfunction, calcium overload, and decreased responsiveness of myofilaments to calcium) may play a significant role.[11,15] Although investigators have suggested that calcium channel blockers or free radical scavengers may be useful in the treatment of myocardial stunning, inotropic support of the stunned myocardium until spontaneous recovery occurs remains the mainstay of treatment. Whatever the cause, stunned myocardium results in regions of reperfused, viable, but temporarily dysfunctional myocardium after an acute ischemic event. With sustained reperfusion, there is the potential for recovery of function.

### HIBERNATING MYOCARDIUM

Historically, it was thought that ventricular wall dysfunction in patients with coronary artery disease results from regions of infarcted myocardium. However, with the advent of reperfusion therapies, it came to be recognized that some dysfunctional myocardium can recover after the return of blood flow to ischemic regions.[16,17] It is believed that these regions of *chronically* ischemic myocardium go into a state of "hibernation" in which metabolic activity is downregulated. This represents an adaptive process that reduces oxygen consumption and prevents irreversible ischemic damage.[16–18] Identification of patients with hibernating myocardium is important, because regions of hibernating myocardium consist of viable cells and revascularization may reverse the dysfunction and ameliorate LV failure.

### CARDIOGENIC SHOCK

Acute MI leads to cardiogenic shock through ischemic dysfunction of myocytes and loss of effective contractility. The poor outcomes associated with this syndrome are due, at least in part, to the progressive nature of the dysfunction, in which worsening hypoperfusion leads to increasing ischemic and infarcted regions of myocardium. Cessation of

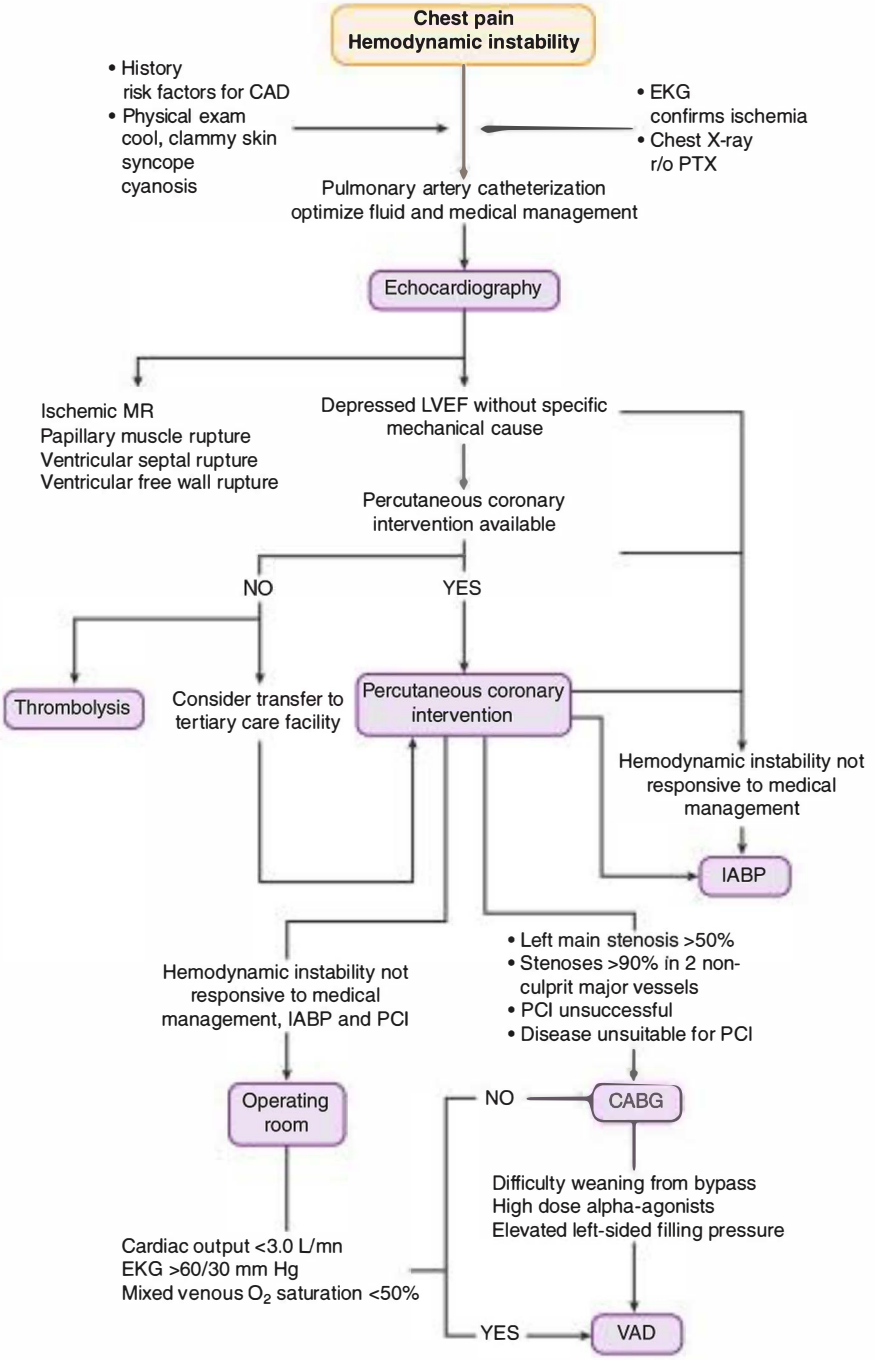



**FIGURE 31-1** Decision-making flowchart: Management of patients in cardiogenic shock. CAD, coronary artery disease; EKG, electrocardiogram; PTX, pneumothorax; PCI, percutaneous coronary intervention; IABP, intra-aortic baloon pump; CABG, coronary artery bypass grafting; VAD, ventricular assist device.

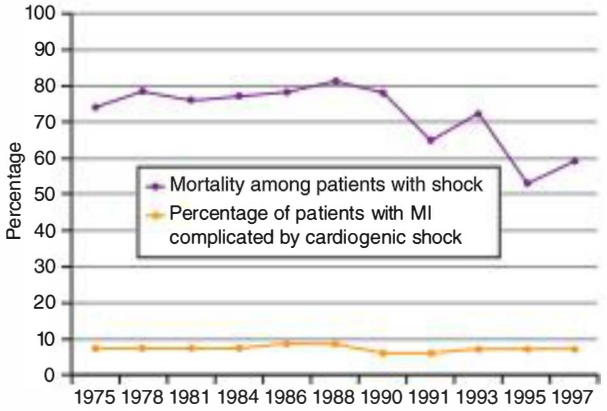



**FIGURE 31-2** Temporal trends in the incidence of cardiogenic shock after myocardial infarction and in mortality among those patients. (Data from Goldberg RJ, Samad NA, Yarzebski J, et al. Temporal trends in cardiogenic shock complicating acute myocardial infarction. *N Engl J Med* 1999;340(15):1162–1168.)

this "vicious cycle" must occur early to increase survival rates in patients who present in cardiogenic shock after MI (Fig. 31-2).

Cardiac function depends on a complex interplay of a variety of factors: myocyte contractility, preload, afterload, and electrical coordination. After myocardial damage, ischemic myocytes lose contractile function. This results in a decrease in stroke volume and cardiac output. To compensate for this loss, sympathetic tone is increased, and this results in tachycardia, systemic vasoconstriction, and increased contractile function in the remaining, nonischemic myocardium. Although these mechanisms help maintain both systemic and coronary perfusion, they also lead to increasing cardiac workload and oxygen consumption in the remaining myocytes.

If the remaining portions of the heart are able to maintain cardiac output and blood pressure, a compensated state may develop that allows for systemic and coronary perfusion without extension of the infarct. However, if the compensatory mechanisms cannot meet the increased demand, the area of ischemic and infarcted myocardium increases, leading to a downward spiral in cardiac function and ultimately to shock. Once mean arterial blood pressure falls below 70 mm Hg, coronary blood flow becomes severely restricted.[19] This spiral toward shock and ultimately death is supported by autopsy studies that have shown that infarcted regions of myocardium contain varying degrees of progression, suggesting an initial insult followed by multiple subsequent infarction events.[20] Traditionally, cardiogenic shock was thought to occur after the loss of approximately 40 percent of LV muscle mass.[21] Although studies have varied in the precise definition of hemodynamic variables, most would include SBP less than 90 mm Hg, cardiac index less than 2.2 L/min/m$^2$, and pulmonary capillary wedge pressure (PCWP) less than 15 mm Hg.[22,23]

### RIGHT VENTRICULAR DYSFUNCTION

Most patients with cardiogenic shock related to ventricular dysfunction have primarily LV failure; in the SHOCK (SHould we emergently revascularize Occluded Coronaries in cardiogenic shoCK) trial, nearly 80 percent of patients presented with shock resulting from predominant LV failure.[24] In contrast, less than 3 percent of patients presented with isolated right ventricular (RV) failure. However, despite younger age and a lower incidence of multivessel disease, a similar mortality rate was observed in the group with RV infarcts.[4] A variety of factors may contribute to this phenomenon, including RV dependence on atrial filling that may be compromised by atrioventricular (AV) dissynchrony, poor RV compensation for ischemia secondary to the large surface area and thin free wall, and concomitant LV dysfunction with loss of septal assistance to RV systole.

### PERIPHERAL EFFECTS

Traditionally, the vicious cycle of ventricular dysfunction was thought to be the primary pathophysiologic process involved in the development of ventricular dysfunction and cardiogenic shock. More recently, data have begun to suggest that the pathophysiology of cardiogenic shock may be more complicated.[25] Patients in the SHOCK trial and registry have been found to have a wide range of ejection fractions with a mean of approximately 30 percent, and systemic vascular resistance (SVR) was not universally elevated despite the use of vasopressors.[23,25–27] Based on studies of nitric oxide species, Hochman[25] concluded that some patients may have a significant component of systemic hypoperfusion related to a systemic inflammatory response caused by the release of inflammatory cytokines, and the SHOCK-2 (Should we inhibit nitric Oxide synthase in patients with Cardiogenic Shock) trial was designed to evaluate additional medical therapies directed toward the inhibition of inflammatory and vasodilatory mediators of shock.[25]

## Clinical Features

Precise estimates of the incidence of cardiogenic shock after acute MI are difficult to obtain because many patients die before reaching medical care. Furthermore, varying definitions of cardiogenic shock may contribute to variation among studies. The early report by Griffith and associates[28] had an incidence of nearly 20 percent; however, more recent studies have shown a consistent incidence of 6 to 10 percent.[2,29–31] The high incidence reported by Griffith may have been due in part to the inclusion of patients with underresuscitated hypovolemic shock in an era before invasive hemodynamic monitoring.[5] Despite advances in the diagnosis and treatment of patients with MI, the incidence of cardiogenic shock in this population over the past three decades has remained relatively constant.[2] Although mortality rates have improved (Fig. 31-2), patients diagnosed with cardiogenic shock during an admission for MI still have a substantially higher

in-hospital mortality rate than do those without shock (59 vs 8 percent).[2,23] Overall cardiogenic shock accounts for more than 55 percent of the in-hospital mortality of MI.[30] In addition, long-term survival of patients with cardiogenic shock remains significantly lower than that in patients without it even after hospital discharge.[32]

Interestingly, although patients may present to the hospital in cardiogenic shock, a significant proportion (anywhere from 44–90 percent) develop shock after admission.[30,33] In-hospital mortality is similar in both groups, although there may be a long-term survival advantage among patients who develop shock after hospital admission.[30,34,35] Median time to the development of shock has varied in reported series from 5 h to nearly 24 h.[24,30,33] This raises the question of whether initial therapies may contribute to the development of cardiogenic shock in some patients and, in light of the high mortality associated with the development of shock (independent of time to onset), suggests the importance of initiating early preventive measures.

The clinical presentation begins with the classic symptoms of MI. With the onset of cardiogenic shock, physical signs of hypoperfusion begin to predominate as oxygen delivery to vital organs becomes impaired: cold and clammy extremities, ashen or cyanotic skin, oliguria, and an altered sensorium.[1] Risk factors for the development of cardiogenic shock include age, diabetes, and a previous MI.[30,36] In addition, studies have demonstrated a correlation between large infarct size (as measured by peak cardiac enzyme levels), anterior MI, a depressed left ventricular ejection fraction (LVEF), and the development of shock.[36,37] Those who had undergone coronary artery bypass grafting (CABG) in the past, however, were less likely to develop shock during their admission.[30]

## Diagnostic Modalities

Assessment of a patient with systemic hypoperfusion should begin with the exclusion of noncardiac causes. Other causes of shock include hypovolemia, sepsis, pericardial tamponade, aortic rupture, tension pneumothorax, and anaphylaxis (Table 31-1). In light of the poor outcomes associated with the onset of cardiogenic shock after MI, initiation of therapies to improve systemic perfusion should not be delayed.

An electrocardiogram (ECG) should be performed immediately. Absence of electrocardiographic changes associated with ischemia essentially excludes the diagnosis of post-MI cardiogenic shock. A chest x-ray will rule out pneumothorax as a cause of circulatory collapse. History and physical examination also should assist in differentiating cardiogenic shock from other causes, such as sepsis, anaphylaxis, and neurogenic. In fact, despite the vast armamentarium of advanced diagnostic tests, physical findings remain significant predictors of in-hospital mortality. In the global utilization of streptokinase and tissue plasminogen activator

**TABLE 31-1: Clinical Presentation of Different Etiologies of Shock**

| Cardiogenic Shock | Septic Shock | Anaphylactic Shock | Hypovolemic Shock | Hemorrhagic Shock | Pericardial Tamponade | Tension Pneumothorax | Massive Pulmonary Embolism |
|---|---|---|---|---|---|---|---|
| ***Signs and symptoms*** | | | | | | | |
| Pallor, fainting<br>Cold, clammy skin<br>Arrythmias<br>Oliguria | Fever, chills<br>Warm skin<br>Tachycardia<br>Oliguria | Urticaria, hives<br>Warm skin<br>Tachycardia<br>Oliguria<br>Respiratory distress | Pallor, fainting<br>Cold, clammy skin<br>Tachycardia<br>Oliguria | Pallor, fainting<br>Cold, clammy skin<br>Tachycardia<br>Oliguria | Pallor, fainting<br>Cold, clammy skin<br>Tachycardia<br>Oliguria | Pallor, fainting<br>Cold, clammy skin<br>Respiratory distress<br>Tachycardia<br>Oliguria | Pallor, fainting<br>Tachycardia<br>Respiratory distress |
| ***Laboratory*** | | | | | | | |
| Elevated cardiac enzymes | Elevated white blood cells<br>(+) blood cultures | Eosinophilia | | Decreased hemoglobin, hematocrit | | | |
| ***Electrocardiogram*** | | | | | | | |
| Ischemic changes | Sinus tachycardia | Sinus tachycardia | Sinus tachycardia | Sinus tachycardia | Low-voltage electrical alterans | | Right axis deviation<br>right axis strain |
| ***Chest x-ray*** | | | | | | | |
| Pulmonary vascular congestion | | | | | Pulmonary vascular congestion | Pneumothorax | |

**TABLE 31-2: Hemodynamic Measurements with Different Etiologies of Shock**

| | Cardiogenic Shock | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Biventricular Failure | LV Failure | RV Failure | Septic | Anaphylactic | Hypovolemic or Hemorrhagic | Pericardial Tamponade | Tension Pneumothorax | Massive Pulmonary Embolism |
| BP | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ |
| CO/CI | ⇓⇓ | ⇓⇓ | ⇓⇓ | ⇑⇑ or normal | ⇑ or normal | ⇓ | ⇓ | ⇓ | ⇓⇓ |
| HR | ⇑ | ⇑ | ⇑ | ⇑ | ⇑ | ⇑ | ⇑ | ⇑ | ⇑ |
| SV | ⇓ | ⇓ | ⇓ | ⇑ or normal | ⇑ or normal | ⇑ or normal | ⇓⇓ | ⇓ | ⇓ |
| SVR | ⇑ or normal | ⇑ or normal | ⇑ or normal | ⇓⇓ | ⇓⇓ | ⇑ or normal | ⇑ | ⇑ | ⇑ |
| CVP | ⇑ | ⇑ or normal | ⇑⇑ | ⇓ or normal | ⇓ or normal | ⇓⇓ | ⇑⇑ | ⇑ | ⇑⇑ |
| PAP | ⇑ | ⇓ | ⇓ | ⇓ | ⇓ | ⇓ | ⇑⇑ | ⇓ | ⇑⇑ |
| PCWP | ⇑ | ⇑⇑ | normal or ⇓ | ⇓ or normal | ⇓ or normal | ⇓⇓ | ⇑⇑ | ⇓ | normal or ⇓ |

LV, left ventricular; RV, right ventricular; BP, blood pressure; CO, cardiac output; CI, cardiac index; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance; CVP, central venous pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure.

(tPA) for occluded arteries (GUSTO trials), subjective signs of hypoperfusion were among the most significant predictors of 30-day mortality: altered sensorium [odds ratio 1.68, 95 percent confidence interval (CI) 1.19–2.39], cold clammy skin (1.68, 95 percent CI 1.15–2.46), and decreased urine output (2.25, 95 percent CI 1.61–3.15).[35]

Initial laboratory investigations should focus on evaluating perfusion and oxygenation by measuring arterial blood gas as well as assessing levels of cardiac enzymes and electrolytes and measuring a hematocrit. Levels of cardiac enzymes and hematocrit in particular have prognostic significance in patients with acute MI.[38–42] Invasive monitoring of blood pressure should be initiated rapidly, as noninvasive cuff pressures may underestimate actual pressure significantly in the setting of peripheral vasoconstriction. In the absence of evidence of pulmonary edema (on physical examination or chest x-ray), volume status may be assessed by the patient's response to intravenous (IV) fluid resuscitation. Perhaps most important in the final determination of cardiac function and etiology are pulmonary artery catheterization and echocardiography.

### ECHOCARDIOGRAPHY

Rapid echocardiography (ECHO) is an important tool in the diagnosis and management of patients with cardiogenic shock. It allows for an expedited and accurate assessment of overall cardiac function. Multiple studies have shown that the ejection fraction is an important predictor of outcome even when it is measured within 24 h of presentation.[26,43] In addition, it can exclude other causes of circulatory collapse unrelated to ventricular dysfunction such as pericardial tamponade, IMR, and ventricular free wall or septal rupture, which may require different therapies.

### PULMONARY ARTERY CATHETERIZATION

Placement of a pulmonary artery catheter allows direct measurement of right-sided cardiac pressures and extrapolation to left-sided filling pressures. Patients in cardiogenic shock are expected to have poor cardiac function, with adequate ventricular preload leading to depressed cardiac output and hypotension (Table 31-2). In the setting of ventricular infarction, diastolic dysfunction may contribute to impaired ventricular filling, requiring an even higher PCWP to maintain cardiac output. Even in the absence of hypotension, some patients may have evidence of systemic hypoperfusion (and its accompanying clinical signs); their in-hospital mortality, although lower than that of patients with hypotension (43 vs 66 percent), is high. Although clinical characteristics are important, hemodynamic monitoring should be initiated rapidly to obtain measurements of ventricular preload and cardiac output.

Recently continuous, arterial pressure-based cardiac output measurement devices have been introduced. These devices provide real-time continuous hemodynamic monitoring using an arterial catheter. They can provide data to diagnose and guide treatment while avoiding the cost and complications of pulmonary artery catheters.[44]

## Medical Therapies

As was noted above, therapies should not be delayed while one awaits diagnostic test results. Initial management should be directed immediately toward improving systemic and coronary perfusion and oxygenation. Supplemental oxygen should be delivered, and mechanical ventilation should be initiated when appropriate. Electrical complications of acute MI are common and before the development

of coronary care units, they constituted the most common cause of death.[45] Depending on the location of the infarct, a variety of rhythm disturbances may occur, including tachy- and bradyarrythmias in both the atria and the ventricles. Therefore, telemetry monitoring should be initiated to screen for electrical dysfunction and allow for early treatment. Rapid correction of rhythm disturbances with antiarrythmic agents or cardioversion may be required, as AV dissynchrony may contribute to poor cardiac function. The use of analgesics (morphine sulfate or fentanyl) to control pain is also an important tool in reducing sympathetic tone and thus decreasing preload, afterload, and myocardial work.

## VOLUME RESUSCITATION AND ELECTROLYTE REPLACEMENT

Although cardiac dysfunction accounts for most of the decreased cardiac output and systemic hypoperfusion, relative hypovolemia may coexist in as many as 20 percent of patients with cardiogenic shock.[46] Hemodynamic parameters measured with a pulmonary artery catheter should guide resuscitation efforts. Optimal ventricular filling pressures may vary among patients. Initial infusion with either normal saline or Ringer's lactate is appropriate, although blood products should be used early. In patients over 65 years of age with a hematocrit below 33 percent, blood transfusion during admission with MI is associated with a decrease in 30-day mortality (conversely, patients with an admission hematocrit above 36 percent who received a transfusion had a higher mortality rate).[42] Among patients with a hematocrit below 27 percent who do not receive a transfusion, the mortality rate has been shown to be approximately 50 percent, three times higher than that of patients with a normal hematocrit (above 37 percent).[42] Recently it has been suggested that patients requiring transfusions were more ill at baseline and at increased risk of death.[47] Cardiac myocyte dysfunction is worsened by alterations in the electrolyte and acid–base environment. Maintenance of appropriate electrolyte levels is therefore essential, as is optimizing the patient's acid-base status.

## VASODILATORS

Pharmacologic therapies such as nitrates, angiotensin-converting enzyme (ACE) inhibitors, and β-blockers have proven effectiveness in reducing mortality in patients with MI. However, all these agents have the potential to cause systemic hypotension; their use should be limited in patients in cardiogenic shock. Nitroglycerin has been shown to improve myocardial oxygen delivery and reduce oxygen demand as well as augment the antiaggregatory effects of aspirin on platelets.[48–50] Nitroglycerin also has been shown to reduce ischemia and infarct size. Although it has been difficult to demonstrate a survival benefit among patients treated with nitrates in large trials such as the Grupo Italiano per lo Studio della Sopravivenza nell'infarto Miocardico (GISSI) 3 study,[51] as many as half the patients in the placebo group received off-label nitrates, probably diluting the detection of a real benefit. Also, seven smaller studies demonstrated an impressive reduction (41 percent) in post-MI mortality with the use of nitroglycerin.[52]

Although IV nitroprusside has many of the same pharmacologic effects as nitroglycerin, some differences make it less useful in patients with acute MI; most importantly, it may exacerbate coronary steal by failing to promote collateral blood flow to ischemic myocardium.[53] In light of the salutary effects of nitrates on cardiac work and the potential decrease in mortality, IV nitrate therapy (preferably with nitroglycerin) should be started when systemic arterial blood pressure allows. The initial doses should be low (5–10 mg/min) with rapid titration upward to optimize arterial blood pressure and LV filling pressures (PCWP between 15 and 22 for patients in severe cardiac failure).

## INOTROPIC SUPPORT

If optimization of ventricular filling pressures fails to ameliorate systemic hypoperfusion and hypotension, the use of inotropic support and intra-aortic balloon counter-pulsation (IABP) should be considered. A variety of inotropic agents are available, and the choice of a specific drug should be tailored to the specific clinical and hemodynamic status of the patient, particularly the degree of systemic hypotension.

***Dopamine.*** In patients with an SBP below 80, dopamine is one of the first-line cathecholamines because it has both inotropic and vasoconstrictive effects. Dopamine interacts with a variety of receptors in a dose-dependent manner. These receptors include the dopamine (DA)-1 receptors in the renal vasculature that mediate renal vasodilatation,[54] $\beta_1$-adrenergic receptors in the heart leading to increased inotropy and chronotropy, and α-adrenergic receptors in the peripheral vasculature leading to increased vascular resistance. As the dose increases, the predominant effect changes; however, there are no precise cutoffs, and the response to dopamine may vary between patients.[54]

At low doses (0.5–3.0 μg/kg/min) it acts primarily as a dopaminergic agonist, increasing renal blood flow. At higher doses (3–5 μg/kg/min) β-adrenergic effects become noticeable, although dopaminergic effects still dominate. At these doses, improvement in renal perfusion depends primarily on the increase in cardiac output rather than on dilatation of the renal arterial bed.[55,56] Between 5 and 10 μg/kg/min, β-adrenergic effects become dominant and α-adrenergic effects become noticeable. Finally, in the range of 10 to 20 μg/kg/min, dopamine functions primarily as an α-adrenergic agent, leading to significant peripheral vasoconstriction. At doses above 20 μg/kg/min, coronary vasoconstriction may predominate.[52]

Many of the presumed renal protective effects of low-dose dopamine have come under attack recently.[54,57] The renal vasodilatation thought to be related to dopaminergic stimulation actually may be due to augmentation of cardiac output through both increased stroke volume and increased heart

rate.[58] Thus, dopamine should be used with care in patients in cardiogenic shock, in whom the increased inotropy may increase myocardial oxygen demand beyond the increase in oxygen delivery, leading to further ischemia; this is particularly of concern at high doses, in which case coronary vasoconstriction may lead to infarction of at-risk myocardium. In fact, the recently published SOAP II study demonstrated that patients in shock treated with dobutamine were at increased risk of developing arrhythmias, and patients in cardiogenic shock treated with dobutamine had a significantly increased mortality at 28 days when compared with patients given norepinephrine.[59] However, dopamine remains an important agent in the initial management of hypotension unresponsive to fluid resuscitation, and the necessity for high-dose dopamine should lead to the insertion of an IABP to protect myocardium at risk for further ischemia and infarction.

***Dobutamine.*** In contrast to dopamine, dobutamine causes peripheral vasodilatation in association with its inotropic effects. Therefore, it is best used in patients with SBP greater than 80. Dobutamine originally was thought to be a selective $\beta_1$-adrenergic agonist, but it now is recognized that it also has $\alpha$- and $\beta_2$-adrenergic effects. As with dopamine, the relative importance of these effects changes with the dose.[5] At rates between 2.5 and 15 mg/kg/min, dobutamine increases cardiac output without significantly affecting peripheral vascular resistance (probably as a result of stimulation of both $\alpha_1$-mediated vasoconstriction and $\beta_2$-mediated vasodilatation).[60] At higher doses, $\alpha_1$-adrenergic effects may begin to predominate with an increase in heart rate, LV afterload, and myocardial oxygen demand. In contrast, at lower doses, myocardial oxygen demand may remain constant despite increased contractility because of the reduction in peripheral vascular resistance, ventricular volumes, and wall stress.[61]

***Isoproterenol.*** Isoproterenol is a $\beta$-adrenergic agonist used primarily in the treatment of postcardiotomy cardiogenic shock. It has both an inotropic and a chronotropic effect on the heart and results in systemic vasodilatation. The increase in cardiac output seen with isoproterenol infusion is due largely to a resultant increase in heart rate.[62] Because heart rate is a major determinant of myocardial oxygen demand, isoproterenol infusion may increase myocardial oxygen consumption.[63] In addition, it has been shown to shunt blood from ischemic myocardium to nonischemic areas.[64] This also results in an increase in ventricular instability that may result in ventricular arrhythmias even at relatively low doses.[63] In light of these problems, the use of isoproterenol in the setting of post-MI cardiogenic shock largely has been abandoned. It may have some application in a hypotensive patient with bradycardia, but transvenous pacing is preferred.

***Phosphodiesterase Inhibitors.*** Milrinone and amrinone are nonadrenergic inotropic agents. In addition, they have peripheral and pulmonary vasodilatory effects. Although they have minimal chronotropic and arrhythmogenic actions compared with the cathecholamines,[64] they also have long half-lives. This mitigates their usefulness in the acute post-MI setting. Therefore, they are used only when other agents have proved ineffective.[65,66] Most commonly, this occurs in the setting of right-sided heart failure, in which the increased pulmonary vasodilation of these agents has added benefit.

## VASOPRESSORS

In patients without adequate arterial blood pressure, vasopressor agents may be required to maintain systemic perfusion.

***Norepinephrine.*** Norepinephrine is a combined $\alpha$- and $\beta$-adrenergic agonist. At low doses, its effects include primarily increased cardiac output and arterial blood pressure (mainly $\beta$-adrenergic-mediated).[67] At higher doses, vascular resistance is markedly increased and cardiac output actually may fall. Treatment with norepinephrine in patients with cardiogenic shock results in rapid increases in blood pressure, vascular resistance, and the LV stroke work index.[63] The last effect presents the main downside to norepinephrine in the setting of post-MI shock. Although the increased blood pressure improves myocardial oxygen supply through increased coronary blood flow,[68] the increase in the stroke work index increases oxygen demand in a potentially ischemic heart. While a shift from anaerobic to aerobic metabolism was observed with norepinephrine infusion in patients with cardiogenic shock, myocardial oxygen extraction remained abnormally high.[68] Other side effects of norepinephrine infusion include aggravation of oliguria through constriction of the renal arterial supply, increased risk of ventricular arrhythmias, and peripheral ischemia and limb loss. Despite these drawbacks, norepinephrine is a potent vasopressor with a rapid onset; its use is appropriate in severely hypotensive patients to maintain mean arterial pressure in the range of 70 to 80 mm Hg while other therapies are instituted.

***Vasopressin.*** Arginine vasopressin has been used frequently in patients with vasodilatory shock. In a variety of circumstances that include septic shock and postcardiotomy vasodilatory shock, an endogenous vasopressin deficiency exists.[69,70] Although that deficiency has not been seen in small series of patients in cardiogenic shock,[69] the recent recognition of a possible vasodilatory component in some patients in the SHOCK trial[25] may indicate a role for vasopressin in this setting. Traditionally, vasopressin was thought to have a negative impact on coronary perfusion; however, this was based on experimental data in normotensive dogs. Data in hypotensive models suggest that vasopressin increases coronary perfusion.[71,72] In addition, clinical trials in critically ill patients with vasodilatory shock suggest that the use of a vasopressin infusion results in decreased norepinephrine requirements, an improved cardiac index, a decreased stroke work index, and better preservation of gastric perfusion.[73] Although further study is necessary, vasopressin may provide a useful adjunct to norephinephrine in the maintenance of systemic blood pressure during the

initial phase of cardiogenic shock before the institution of more definitive therapies.

None of the pharmacologic agents listed above has been shown to have a survival benefit in the treatment of cardiogenic shock. They all have significant side effects, and any attempt to increase cardiac output or systemic blood pressure in an attempt to increase coronary perfusion carries a risk of increasing myocardial ischemia. The use of vasopressors should be limited to keep mean arterial pressure at 70 to 80 mm Hg, not to return patients to a normotensive state, and inotropes should be used sparingly and under careful monitoring of hemodynamic parameters. In all cases, the most appropriate uses of these agents are as temporizing measures until the initiation of IABP placement, mechanical circulatory support, and revascularization.

## THROMBOLYSIS

The improvement in outcome with thrombolysis in patients with acute MI has been well established,[74–76] but in patients with cardiogenic shock, the benefits of this therapy are less clear. Many studies explicitly excluded patients with cardiogenic shock, and even more failed to describe the inclusion or exclusion of those patients.[74,77,78] Thrombolytics may decrease the incidence of the subsequent development of cardiogenic shock,[75,76,79] but no trial has demonstrated a convincing reduction in mortality in patients with already established cardiogenic shock.

Mathey and associates reported the survival of three patients with cardiogenic shock treated with streptokinase in 1980.[80,81] In a larger series of 44 patients, however, mortality remained at 66 percent.[82] The GISSI-1 trial randomized a total of 280 patients with cardiogenic shock. Overall mortality in that group was 70 percent and did not differ between those treated with streptokinase (69.9 percent) and controls receiving placebo (70.1 percent).[75] Mortality rates were similar in trials comparing various thrombolytic regimens: The International Study Group reported mortality rates of 78.1 and 64.9 percent among 246 patients with cardiogenic shock treated with tPA or streptokinase[83]; the GUSTO trial also had a high 30-day mortality among 2972 patients treated with streptokinase (51 percent) or tPA (57 percent).[30]

Interestingly, among the 44 patients in the Society for Cardiac Angiography registry, arterial patency was achieved in only 19 patients (44 vs 71 percent in the registry as a whole), among whom mortality dropped to 42 percent (vs 84 percent in patients without reperfusion, $p = 0.0005$). In the GUSTO trial, lytic therapy was less likely to be successful in patients with cardiogenic shock [Thrombolysis in Myocardial Infarction (TIMI) 0 or 1 flow 42.9 vs 27.7 percent, $p < 0.001$].[34] However, with successful reperfusion, mortality can be decreased significantly.[34,82,84] Thus, the poor performance of thrombolysis in the setting of cardiogenic shock may be secondary to an inability to achieve patency.

The decreased ability of thrombolysis to achieve successful reperfusion in the setting of cardiogenic shock is not completely understood and probably involves a combination of hemodynamic, metabolic, and mechanical factors.[85] Hypotension and coronary hypoperfusion probably play a significant role. In the setting of cardiogenic shock, research in canine models has suggested that the rate and degree of thrombolysis after intracoronary injection of tPA are depressed compared with those in normotensive controls,[86,87] and in clinical trials, hypotension was associated with lower TIMI flow grades after thrombolysis.[88] The augmentation of blood pressure through vasopressors or an IABP may improve the success rate of thrombolysis in patients with cardiogenic shock.[87,89,90]

Despite these limitations, thrombolysis remains an important treatment for acute ST-elevation MI when percutaneous catheter-based interventions are not available. Indications and contraindications for thrombolytic therapy are well established (Table 31-3).[91] However, recent data suggest that even when percutaneous catheter-based interventions are unavailable, transport to a facility with those services improves survival and decreases complications.[92] Furthermore, the use of IABPs (see below) to stabilize patients for transport to a tertiary care facility has been shown to be a safe alternative to treatment with thrombolytics.[66] Although thrombolysis is an option in limited circumstances, mechanical revascularization delivers the best outcomes in acute MI patients.

## INTRA-AORTIC BALLOON COUNTERPULSATION

In 1958, Harken described a mechanism for diastolic augmentation of blood flow.[93,94] However, initial attempts to use femoral–femoral bypass to augment diastolic flow met with technical difficulties, including the need for bilateral femoral arteriotomies and problems with the extracorporeal pump. Efforts at demonstrating increased cardiac perfusion failed. However, after work by Moulopoulos and associates[95,96] in 1968, Kantrowitz and coworkers described the first use of an IABP to provide diastolic flow augmentation in patients with cardiogenic shock.[97] Initial models required operative placement via a femoral arteriotomy, but in 1979 Bregman and Casarella introduced a percutaneously placed model inserted through a 12F sheath.[98] Further refinements have included a dual-lumen design, wire-guided placement, reduced sheath sizes (8F or 9F for 30–50-mL balloons), and the use of helium to inflate and deflate the balloon rapidly.[99,100]

Most commonly, the IABP is inserted percutaneously into the femoral artery, using a modified Seldinger technique. After puncture of the artery, a J-wire is advanced into the aorta. The needle is removed, and the IABP catheter is inserted over the wire into the descending aorta. When properly placed, the balloon should lie immediately distal to the origin of the left subclavian artery (Fig. 31-3). In specialized cases such as pediatric patients and those with significant peripheral vascular disease that precludes the use of the femoral artery, other insertion sites may be used, including the ascending aorta, aortic arch, and subclavian, axillary, and iliac arteries.[101–107]

## TABLE 31-3: Indications and Contraindications for Thrombolysis

***Indications***

Clinical history and presentation strongly suggestive of myocardial infarction within 6 h plus one or more of the following:
1 mm ST elevation in two or more contiguous limb leads
2 mm ST elevation in two or more contiguous chest leads
New left bundle branch block
2 mm ST depression in $V_{1-4}$ suggestive of true posterior myocardial infarction
Patients presenting with above within 7–12 h of onset with persistent chest pain and ST-segment elevation
Patients age <75 years presenting within 6 h of anterior wall myocardial infarction should be considered for recombinant tissue plasminogen activator

***Contraindications***

Absolute
Aortic dissection
Previous cerebral hemorrhage
Known history of cerebral aneurysm or arteriovenous malformation
Known intracranial neoplasm
Recent (within 6 months) thromboembolic stroke
Active internal bleeding (excluding menstruation)
Patients previously treated with streptokinase or an isolated plasminogen streptokinase activator complex (APSAC or anistreplasse) shoud receive tissue plasminogen activator, reteplase, or tenecteplase
Relative
Severe uncontrolled hypertension (blood pressure >180/110 mm Hg) on presentation or chronic severe hypertension
Current use of anticoagulants or known bleeding diathesis
Recent (within last 2–4 weeks) trauma, including head injury or traumatic or prolonged (>10 min) cardiopulmonary resuscitation
Recent (within 3 weeks) major surgery, organ biopsy, or puncture of noncompressible vessel
Recent (within last 6 months) gastrointestinal or genitourinary or other internal bleeding
Pregnancy
Active peptic ulcer disease

Adapted from Lip GY, Chin BS, Prasad N. ABC of antithrombotic therapy: Antithrombotic therapy in myocardial infarction and stable angina. *BMJ* 2002;325(7375): 1287–1289.

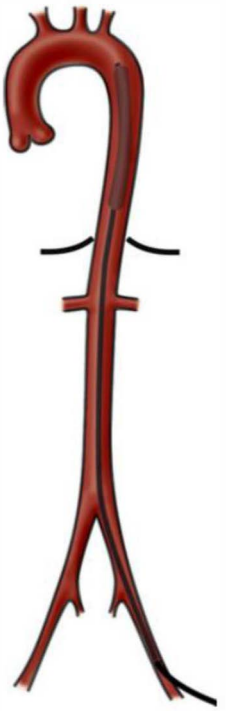


**FIGURE 31-3** Schematic diagram of intra-aortic balloon pump placement. The balloon tip should be placed distal to the take-off of the left subclavian artery.

After insertion, the balloon is connected to a pump console that controls its inflation and deflation. The timing of these events is synchronized to the patient's cardiac cycle through the use of either electrocardiographic or aortic pressure-sensitive timing. The balloon inflates with the onset of diastole, displacing blood both proximally and distally and increasing intra-aortic pressure (diastolic augmentation). Immediately before systole, the balloon deflates, reducing obstruction to LV ejection (decreased afterload). With electrocardiographic timing, balloon inflation occurs (Fig. 31-4).

The decreased afterload results in a reduction in end-diastolic LV diameter and volume and a reduction in ventricular wall stress; a slight decrease in heart rate also is seen.[108] Multiple studies have shown that, as expected, the reductions in wall stress and heart rate, lead to a decrease in myocardial oxygen demand and consumption.[109] Through diastolic augmentation, the IABP increases coronary perfusion and myocardial oxygen delivery.[110] This increase in coronary blood flow has been observed in both hypotensive animals and patients with cardiogenic shock (Fig. 31-4).[109,111] Overall, these effects lead to improved hemodynamics (increased cardiac output, decreased PCWP, improved arterial blood pressure, and improved urine output)[112–114] along with improvement in myocardial metabolism (as reflected in decreasing oxygen extraction and a shift toward aerobic metabolism).[68]

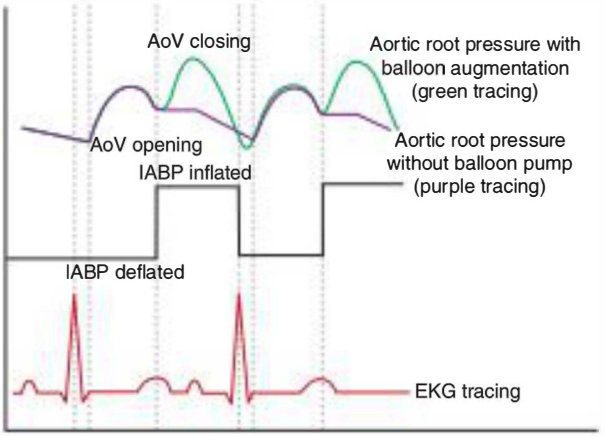



**FIGURE 31-4** Timing of balloon pump inflation and deflation. Deflation is timed to occur just before the QRS complex to reduce afterload maximally as the aortic valve opens. Inflation occurs at the dicrotic notch (corresponding to the peak of the T wave on the ECG). Augmentation of diastolic aortic pressure with balloon inflation is shown by the dark red tracing. IABP, intra-aortic balloon pump; EKG, electrocardiogram.

Despite these improvements in hemodynamic performance and myocardial metabolism, initial results with the IABP alone in the treatment of cardiogenic shock failed to demonstrate improvement in survival.[115,116,117] In a small randomized trial (30 patients) that compared optimal medical therapy for cardiogenic shock with IABP, in-hospital mortality was similar in both groups (50 percent with IABP vs 44 percent with medical management).[115] However, when IABP is combined with revascularization (via thrombolysis, angioplasty, or surgery), it appears that IABP improves both short- and long-term survival, though patient selection remains a confounding factor in these trials. As was noted above, in the setting of cardiogenic shock or hypotension, the rate and degree of thrombolysis are depressed.[87] Additional work with canine models demonstrated improvement in the rate and degree of thrombolysis as well as the time to reperfusion when IABP was added to thrombolytic therapy.[89,90] Observational studies in humans confirmed an advantage for IABP when it was used with thrombolytics.[118,119]

The GUSTO-1 trial was a large randomized trial that investigated the benefits of thrombolysis. In this trial, analysis of patients with cardiogenic shock who had an IABP placed on hospital day 0 or 1 showed a trend toward improved short-term survival (30-day mortality 48 vs 59 percent) when IABP was used and a significant reduction in 1-year mortality (57 vs 67 percent, $p = 0.04$).[120] The trend toward improved 30-day mortality with IABP remained when only patients undergoing revascularization were analyzed (47 vs 64 percent).[120] However, the 310 patients included were not randomized to IABP therapy, and the IABP group had significantly higher use of inotropes, pacemakers, pulmonary artery catheters, diagnostic angiography, and revascularization (both percutaneous and surgical). Most of the difference in survival occurred in the first days; this might have been due to earlier use of IABP but also might have resulted from selection of patients with a better prognosis for more aggressive interventions (including IABP and revascularization).

The larger SHOCK registry included nearly 900 patients who were collected prospectively but not randomized. Analysis of this group showed that patients with IABP use had lower in-hospital mortality than did those without it whether thrombolysis was used (47 vs 63 percent) or not (52 vs 77 percent).[121] Unfortunately, these data also were subject to significant selection bias, and the groups that had the best outcomes included those individulas who underwent revascularization regardless of the adjunctive treatment (thrombolysis with or without IABP support) they received. These results were supported by an analysis of the 23,180 patients with cardiogenic shock enrolled in the National Registry of Myocardial Infarction-2. In this group, use of IABP improved 30-day survival in patients receiving thrombolytics (adjusted odds ratio 0.82; 95 percent CI 0.72–0.93), but a slight increase in mortality was noted in patients undergoing percutaneous coronary angioplasty (PTCA) who had placement of an IABP.

These data suggest that the improvement in thrombolysis noted in the canine models when IABP was used for patients in cardiogenic shock may result in a real improvement in outcomes in those patients.[89,90] For patients not receiving thrombolysis, significant patient selection bias exists in all these studies; however, it is clear that IABP alone does not improve survival over medical therapy. Its use, as with inotropic support, should be as an adjunct to maintain systemic and coronary perfusion and minimize infarct expansion before revascularization. Thus, in hospitals without cardiac catheterization capability, stabilization with IABP and transfer to a tertiary care facility may be the best option.[66] Although selection bias is again a confounding factor, retrospective analysis has suggested improvement in community hospital survival (93 vs 37 percent, $p = 0.0002$), transfer to a tertiary care center (85 vs 37 percent), and 1-year survival (67 vs 32 percent, $p = 0.019$) with the use of IABP in this setting.[122] A recent retrospective study suggests that placement of an IABP prior to PCI results in decreased in-hospital mortality and incidence of major adverse cardiac events when compared to patients having IABP placed after PCI (19 vs 59 percent and 23 vs 77 percent, $p = 0.007$ and 0.0004, respectively).[123] After revascularization, prophylactic use of IABP for 48 h has been shown to maintain patency of revascularized arteries.[124] Weaning of the IABP should be performed before weaning from inotropic and pressor support except when limb ischemia intervenes.

## Surgical Therapies

Multiple studies have shown that the patency of an infarct-related artery is an important predictor of LV function and mortality after acute MI.[125–131] In addition, most studies have

demonstrated worse outcomes with increasing time between symptom onset and reperfusion.[74,75,125,132] These findings were extrapolated to patients with cardiogenic shock, supporting an aggressive approach to early *mechanical* reperfusion for patients in shock after MI. Recently, prospective, randomized data in patients with post-MI cardiogenic shock have become available to define further the indications for and outcomes with emergent revascularization.

## ANGIOPLASTY

The SHOCK trial enrolled 302 patients with post-MI cardiogenic shock resulting from LV dysfunction and randomized them to receive either optimal medical management (including IABP and thrombolysis) or emergent mechanical revascularization [either percutaneous coronary intervention (PCI)(PTCA with or without stenting) or coronary artery bypass surgery]. Revascularization in this group occurred on average within 1 h of randomization for patients undergoing PTCA and within 3 h for those undergoing CABG. There was a trend toward improved 30-day mortality in the revascularization group (46.7 vs 56.0 percent, $p = 0.11$) and a significant reduction in 6-month mortality (50.3 vs 63.1 percent, $p = 0.027$) and 1-year mortality (53 vs 66 percent, $p = 0.025$).[23,43,133] Patients who had successful angioplasty (TIMI grade 2 or 3[134]) had very low mortality rates at 30 days (38 vs 79 percent, $p = 0.003$), and no patient who had a post-PCI occluded infarct artery survived (Fig. 31-5).[23,135] The only group that did not appear to benefit from a strategy of emergent revascularization were those over age 75 (30-day mortality 75.0 vs 53.1 percent, $p = 0.01$), although these results may have been affected by patient selection and a 25-percent revascularization rate before discharge among medically treated patients[23] and have been called into question by results from other studies.[136] The survival advantage seen in the early revascularization group remained at 3 and 6 years.[137] The importance of reducing time to reperfusion in patients with cardiogenic shock after MI has been reinforced by other nonrandomized studies.[138,139] In fact, the goal time period from presentation to the hospital to angioplasty balloon inflation (door-to-balloon time) is 90 min.[140] Significant predictors of poor outcomes in all patients include severity of MR,[26] initial TIMI flow, and culprit vessels other than the right coronary artery.[43]

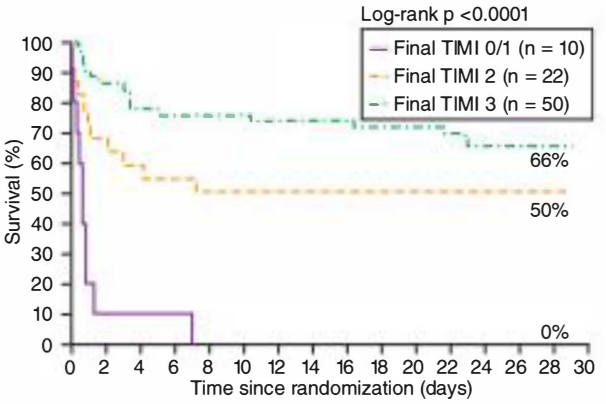



**FIGURE 31-5** Mortality after emergent percutaneous coronary intervention for postinfarction cardiogenic shock stratified by Thrombolysis in Myocardial Infarction (TIMI) flow grade. TIMI, thrombolysis in myocardial infarction. (From Webb JG, Lowe AM, Sanborn TA, et al. Percutaneous coronary intervention for cardiogenic shock in the SHOCK trial. *J Am Coll Cardiol* 2003;42(8):1380–1386.)

## STENTING

Percutaneous coronary stenting has been shown to improve outcomes and reduce angiographic restenosis during elective PTCA.[141–144] Although there was initial reluctance to use stents in the setting of a potentially unstable coronary thrombus, randomized studies have demonstrated that stenting in the setting of acute MI can be performed safely.[145] Unfortunately, the largest studies have failed to demonstrate a survival benefit from the use of stenting in the setting of MI and instead have shown a trend toward increased mortality with the use of primary stenting (although some have shown reductions in combined endpoints such as recurrent ischemia, infarction, and angina).[144,146,147] However, none of these studies included patients with post-MI cardiogenic shock.

Among patients with cardiogenic shock, Antoniucci and associates described a short- and long-term survival advantage to stent placement over angioplasty alone; however, again, selection bias may have played a role in those patients.[148] Similar results to those for MI alone have been obtained in other nonrandomized trials.[149] The Global Registry of Acute Coronary events has provided observational data that suggest an improvement in outcomes (PCI with stenting predicted hospital survival: odds ratio 3.99, 95 percent CI 2.41–6.62).[150] Thus, some evidence exists to support the use of stents in patients with cardiogenic shock; even without strong prospective evidence, it has become common practice (as many as 85 percent of the patients enrolled in the SHOCK trial between 1997 and 1998[135]). A prospective observational study utilizing the National Registry of Myocardial Infarction examined almost 300,000 patients presenting with ST elevation MI and cardiogenic shock. It was seen that patients undergoing primary PCI had decreased odds of death during the index hospitalization (odds ratio, 0.46; 95 percent CI, 0.40–0.53).[151] Further prospective, randomized investigations are needed to define the indications for stent placement in patients with MI and cardiogenic shock.

***Antiplatelet Agents.*** Among patients who have stents placed after MI, antiplatelet agents have become standard practice, as they appear to reduce short-term restenosis and the need for repeat revascularization.[152–155] In nonrandomized trials, combination treatment with abciximab (a glycoprotein IIb/IIIa inhibitor) decreased 1-month overall mortality (18 vs 42 percent, $p = 0.020$) and improved TIMI flow in the infarcted artery compared with stenting

alone.[156,157] However, these mortality rates are low, suggesting that the population studied may have been selected for more aggressive treatment. Additional large randomized trials are needed to assess the impact of adding antiplatelet agents to percutaneous stenting of stenosed arteries in patients with acute MI with cardiogenic shock. Currently all patients receiving drug eluting stents (DES) are placed on antiplatelet therapy for at least 1 year, as they are at increased risk for late in-stent thrombosis, a catastrophic complication.[158–161]

## CORONARY ARTERY BYPASS

Early outcomes with CABG in the setting of acute MI were poor,[162,163] but surgical revascularization within 6 h has shown to improve survival compared with medically treated patients.[164–169] These reports, however, were published as medical management was changing: Randomized trials were evaluating the efficacy of thrombolysis and PCIs in post-MI patients.[75,76,170] Unfortunately, CABG was not included in these studies. Furthermore, subsequent improvements in both interventional and surgical techniques may make comparisons to contemporary populations and treatments meaningless. Thus, the appropriate use of CABG in the setting of MI in general and cardiogenic shock in particular remains a matter of debate.

The results of the SHOCK trial demonstrated that early revascularization improved survival, and despite more severe disease, mortality in the group receiving CABG (guidelines for the use of emergent CABG included left main stenosis equal to or greater than 50 percent, stenoses greater than 90 percent in two nonculprit major vessels, and patients in whom PCI was unsuccessful or who had disease unsuitable for PCI) was similar to that in patients undergoing percutaneous interventions.[23] Large observational studies support the selective use of CABG in patients with cardiogenic shock; although patients in Killip class IV have seven times the CABG-associated mortality of those in Killip class I, mortality in this group is 27 percent, substantially lower than that in patients who do not receive revascularization and comparable to survival in patients undergoing PCI.[171] Although surgery within 3 days of transmural and 6 h of nontransmural MI has been associated with a higher mortality rate (Table 31-4),[172,173] Lee and associates documented decreased early mortality rates when operation occurs before 18 h in patients with cardiogenic shock (7 vs 31 percent).[174] Thus, in patients with ongoing ischemia or cardiogenic shock that is not amenable to medical stabilization, early revacularization with CABG is indicated; however, when possible, surgery should be delayed, especially in patients with transmural infarction.

Unfortunately, randomized data are not available, and the optimal indications for CABG in the setting of MI and cardiogenic shock remain ill-defined. In light of the excellent results obtained with thrombolysis and percutaneous revascularization, CABG probably will not become a primary therapy after MI whether or not cardiogenic shock intervenes; instead, it is best reserved for specific indications for which percutaneous revascularization is unsuccessful or inappropriate. One such indication for CABG surgery may be cardiogenic shock in the setting of left main coronary artery infarction. A recent study demonstrated that patients undergoing CABG in this situation had better survival at 30 days than those having PCI, 40 percent in the surgical group ($n = 6$) and 16 percent in the PCI group ($n = 15$; $p = 0.03$).[175] In addition, current American College of Cardiology/American Heart Association Guidelines Committee recommendations for initial reperfusion therapy in patients with three-vessel coronary disease in cardiogenic shock from AMI is CABG.[176]

**TABLE 31-4: Comparison of Hospital Mortality with Respect to Time of Operation**

| | *Mortality* | |
|---|---|---|
| **Time between CABG and MI** | **Transmural MI (%)** | **Nontransmural MI (%)** |
| <6 h | 12.1 | 11.5 |
| 6–23 h | 13.6 | 6.2[a] |
| 1–7 days | 4.3 | 3.5 |
| 8–14 days | 2.4 | 2.7 |
| ≥15 days | 2.6 | 2.7 |

CABG, coronary artery bypass grafting; MI, myocardial infarction.

[a] $p = 0.006$ nontransmural vs transmural.

Adapted from Lee DC, Oz MC, Weinberg AD, et al. Optimal timing of revascularization: Transmural vs nontransmural acute myocardial infarction. *Ann Thorac Surg* 2001;71(4):1197–1202; discussion 202–204.

***Perioperative Considerations.*** When emergent revascularization by CABG is indicated, timing is important and rapid transport to the operating room is critical; however, some techniques are available to assist in maintaining coronary and systemic perfusion during transport. As was noted above, the use of IABP is preferable to the use of inotropes and vasopressors because of the improvement in myocardial oxygenation and workload. In patients with circulatory collapse, percutaneous cardiopulmonary bypass (CPB) may be initiated via the femoral artery and vein. Flow rates of 3.5 to 5.0 L have been obtained with this method.[177]

Once the patient is in the operating room, anesthetic induction may lead to catastrophic hypotensive circulatory collapse. It is important that both surgery and perfusion teams be prepared for decompensation before the onset of anesthesia. Although the specific type of anesthetic agent used does not appear to alter myocardial oxygen utilization efficiency significantly,[178] a rapid narcotics-based regimen has been recommended.[179] Rapid institution of CPB to provide perfusion to threatened myocardium is essential.

Patients undergoing emergent CABG have high mortality rates; bleeding may contribute to that rate by decreasing

myocardial oxygen delivery. In addition, release of cytokines in response to large-volume transfusions as well as thromboxane $A_2$ release during CPB may worsen coagulopathy, pulmonary hypertension, and myocardial microvascular contraction responses worsening ventricular ischemia.[183]

The choice of a conduit should not be altered from that for elective cases. Although most surgeons use saphenous vein grafts (SVGs) to minimize bypass time, internal mammary artery (IMA) grafting has not been associated with increased complications compared with saphenous vein grafting even in the setting of cardiogenic shock, and late results with IMA grafts are significantly better than those with SVG.[184-186] To reduce MI, harvesting of the IMA can be performed after the initiation of CPB, cross-clamping, and cardioplegia.

In all cases, both antegrade and retrograde cardioplegia should be used for myocardial protection to ensure the delivery of cardioplegia to ischemic areas. Both antegrade and retrograde catheters can be placed before placement of the aortic cross-clamp to ensure rapid delivery of cardioplegia to the entire myocardium. The placement of a "bail-out" catheter across stenotic regions during PCI may assist in the delivery of cardioplegia to ischemic regions.[177] Various authors have advocated a variety of techniques for myocardial protection, including hypothermic fibrillatory arrest,[187,188] oxygenated crystalloid cardioplegia,[187,189] blood cardioplegia,[190,191] and substrate-enriched blood cardioplegia.[187,190] However, in a series of experimental studies, Buckberg and coauthors developed specific modifications of the reperfusion process that reduce myocardial oxygen demand and reperfusion injury in ischemic myocardium. These experimental studies subsequently were validated clinically.[191] Conditions favoring recovery of ischemic myocardium include the following: Decompression of the heart, which reduces myocardial oxygen demand by approximately 50 percent[192]; cardioplegic arrest reduces oxygen demand by approximately 90 percent compared with a beating heart[193]; myocardial metabolism is enhanced by warm blood cardioplegia that maintains normal energy production while decreasing energy demands[194]; low perfusion pressure reduces postischemic edema[195]; and prolonged reperfusion with cardioplegic arrest permits resuscitation of energy-depleted myocardium.[196] Therefore, the standard Buckberg protocol should be used to maximize myocardial protection in patients undergoing CABG who are in cardiogenic shock. This includes induction of cardioplegia with substrate-enriched warm blood cardioplegia for 3 to 5 min, followed by cold blood cardioplegia for 2 to 3 min and then by periodic small-volume infusions. In addition, an infusion of warm blood cardioplegia before removal of the cross-clamp ("hot shot") may improve myocardial recovery.[197]

The occluded artery supplying the largest region of ischemic but viable myocardium should be reperfused first. When vein grafts are used, after completion of the distal anastomosis, regional blood cardioplegia can be delivered to the ischemic area through a side branch of the graft while the proximal anastomosis is completed.

## VENTRICULAR ASSIST DEVICES AND HEART TRANSPLANTATION

In patients with cardiogenic shock refractory to maximal medical management and unimproved by percutaneous intervention or an IABP, implantation of a ventricular assist device (VAD) is a potentially lifesaving maneuver. Two classes of patients may benefit from the use of a VAD: (1) patients with stunned myocardium as a bridge to recovery and (2) patients with extensive infarction requiring a bridge to heart transplantation. Outside clinical trials, VADs are approved for use in patients pending transplantation; therefore, all patients should fulfill the general criteria for transplant recipient selection (Table 31-5).[198] Although complete evaluation is usually impossible in the acute setting, patients with obvious contraindications to transplantation (irreversible neurologic defects, coexisting active neoplasm, etc.) should not be considered for VAD implantation.

When used as a bridge to recovery for myocardial stunning, VAD implantation should be accompanied or preceded by mechanical revascularization, whether percutaneous or surgical. In this setting, the use of short-term VAD is appropriate. VADs suitable for short-term implantation include the Bio-medicus centrifugal pump and the Abiomed and Thoratec pumps. Although the centrifugal pump is easy to insert, it has a significant incidence of thromboembolic complications despite systemic heparinization, and its use largely has been supplanted by use of the pump devices.[199] The Abiomed VAD (AB5000) is a system recently approved by the Food and Drug Administration that consists of a fully automatic, vacuum-assisted console and a paracorporeal, pneumatically driven blood pump. The VAD is designed for short or intermediate termuse. The Thoratec pneumatically driven extracorporeal pump is also suitable for left, right, or biventricular short-term support and has the advantage of allowing significant patient mobility. Both devices require systemic anticoagulation. Percutaneous devices, such as the Abiomed Impella and the Cardiac Assist TandemHeart Pump, are being placed as a bridge to long-term VAD placement and bridge to recovery.[200,201]

In patients with large infarcts without the potential for myocardial recovery, the insertion of a longer-term VAD is required as a bridge to transplantation. Historically, the two most commonly used pulsatile devices were the Heartmate XVE and Novacor pumps. Both are wearable, pulsatile intracorporeal VADs with only a driveline traversing the skin. The Heartmate has the advantage of requiring only aspirin for antiplatelet activity, not systemic anticoagulation; this is achieved through the use of textured blood contact surface that forms a stable biological lining that is resistant to thrombus formation.[202] The Novacor device was discontinued by its manufacturer, World Heart in 2008. It was the first mechanical circulatory support device to support a single patient for more than 6 years.

Other devices with different pump mechanisms have been developed (Table 31-6). The Heartmate II, a continuous-flow VAD, was approved for bridge to transplantation use in 2007. Direct comparison of the Heartmate XVE and II

## TABLE 31-5: Indications and Contraindications for Heart Transplantation in the Acute Setting

***Indications***

Indications for cardiac transplantation determined by severity of heart failure despite optimal therapy

Definite indications
- $Vo_2$ max <10 mL/kg/min
- NYHA class IV
- History of recurrent hospitalization for congestive heart failure
- Refractory ischemia with inoperable coronary artery disease and left ventricular ejection fraction <20%
- Recurrent symptomatic ventricular arrhythmias

Probable indications
- $Vo_2$ max <14 mL/kg/min (or higher with multiple other risk factors)
- NYHA class III–IV
- Recent hospitalizations for congestive heart failure
- Unstable angina not amenable to coronary artery bypass grafting or percutaneous transluminal coronary angioplasty with left ventricular ejection fraction <0.25%

***Contraindications***

General contraindications
- Presence of any noncardiac condition that would shorten life expectancy or increase the risk of death from rejection or complications of immunosuppression

Specific contraindications[a]
- Age >65 years (varies with the program)
- Active infection
- Active ulcer disease
- Severe diabetes mellitus with end-organ damage
- Severe peripheral vascular or cerebrovascular disease
- Coexisting neoplasm
- Morbid obesity
- Creatine clearance <40–50 mL/min, effective renal plasma flow (ERPF) <200 mL/min[b]

Bilirubin >2.5 mg/dL; transaminases >2_normal[c]

Severe pulmonary dysfunction with FVC and $FEV_1$ < ~40% of predicted, especially with intrinsic lung disease

Pulmonary artery systolic pressure >60 mm Hg, mean transpulmonary gradient >15 mm Hg, or pulmonary vascular resistance >5 Wood units[d]
- Acute pulmonary thromboembolism
- Acute diverticulitis
- High risk of life-threatening noncompliance

[a]Contraindications may be either relative or absolute, depending on severity and program preference.

[b]May be suitable for cardiac transplantation if inotropic support and hemodynamic management produce creatinine below 2 mg/100 mL and creatinine clearance above 50 mL/min. Transplantation may be advisable as a combined heart-kidney transplant.

[c]Requires liver biopsy to exclude cirrhosis or other intrinsic liver disease.

[d]Apply only if the increased resistance is largely nonreactive (fixed).

Data from Kirklin JK, McGiffin DC, Pinderski LJ, Tallaj J. Selection of patients and techniques of heart transplantation. *Surg Clin North Am* 2004;84(1):257–287.

## TABLE 31-6: Current Ventricular Assist Devices

| External Centrifugal Pump | External Pulsatile Pump | Internal Pusher Plate Pump | Internal Axial Flow Pump | Total Artificial Hearts |
|---|---|---|---|---|
| Biomedicus ECMO | Abiomed BVS 500<br>Thoratec VAD | Heartmate LVAD<br>Novacor LVAD | Nimbus Intra-Corporeal Assist Device (Heartmate II)<br>DeBakey<br>Micromed | Abiomed TAH<br>Penn State TAH<br>CardioWest TAH |

ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device; LVAD, left ventricular assist device; TAH, total artificial heart.

demonstrated increased survival without disabling stroke or need for device related reoperation [62 of 134 (46 percent) vs 7 of 66 (11 percent), $p$ <0.001], and improved survival rates at 2 years (58 vs 24 percent, $p = 0.008$).[203] After clinical stabilization of the patient, a complete evaluation for heart transplantation can proceed. In light of the potential for discovery of contraindications to transplantation after emergent placement of a VAD, consideration—including discussions with patients and families—must be given to the potential need to withdraw support in patients who are found to be unsuitable recipients for heart transplantation.

## Outcomes and Prognosis

Survival after CABG for patients in cardiogenic shock or those receiving cardiopulmonary resuscitation (CPR) remains poor; 1- and 10-year survival rates are 59.4 and 47.5 percent.[204] However, these rates compare favorably to medical therapy alone, in which mortality rates in excess of 65 percent at 1 year have been reported.[133] Predictors of poor outcomes after CABG in this population include extent of coronary disease, presence of drug-treated diabetes, and lower arterial pH at entry into the operating room.[204]

## Summary

Cardiogenic shock after MI continues to occur in approximately 10 percent of patients who reach the hospital. Though improving slightly, mortality rates remain approximately 60 percent. Patients with hypoperfusion after acute MI should be evaluated rapidly with electrocardiography (ECG), chest x-ray, and echocardiography to determine the cause of shock. In those with cardiogenic shock, therapies should be directed toward stabilization of patients with IV fluid resuscitation, pharmacologic therapy as indicated, and rapid placement of an IABP to support coronary and systemic perfusion. Emergent revascularization with PCI or CABG is associated with improved long-term outcomes. VADs provide an important adjunct to revascularization by supporting circulation through the period of myocardial stunning and providing a bridge to transplantation, and potentially as destination therapy, when appropriate.

# ISCHEMIC MITRAL VALVE DISEASE

## Introduction

Ischemic mitral regurgitation (IMR) is a disease of the ventricle and papillary muscles (PMs) that leads to valvular dysfunction; by definition, the leaflets and valvular apparatus are normal. The frequent coexistence of nonischemic MV disease and coronary artery disease has led to a poor understanding of the natural history and optimal treatment of IMR. In addition, chronic MR may develop after postinfarct LV dilatation, resulting in annular dilatation[205–208]; this may be difficult to differentiate from "functional" MR resulting from dilated cardiomyopathy. MR occurs frequently after acute MI; precise rates have varied from 8 to 50 percent, depending on the modality used to detect the disease.[209–223] This reflects the heterogeneity of IMR. It ranges from clinically silent disease that is identifiable only on Doppler echocardiography or angiography to severe disease that leads to cardiogenic shock and hemodynamic collapse; it may present acutely within hours of the infarct or develop insidiously over years with worsening congestive heart failure (CHF).

### ANATOMIC CONSIDERATIONS

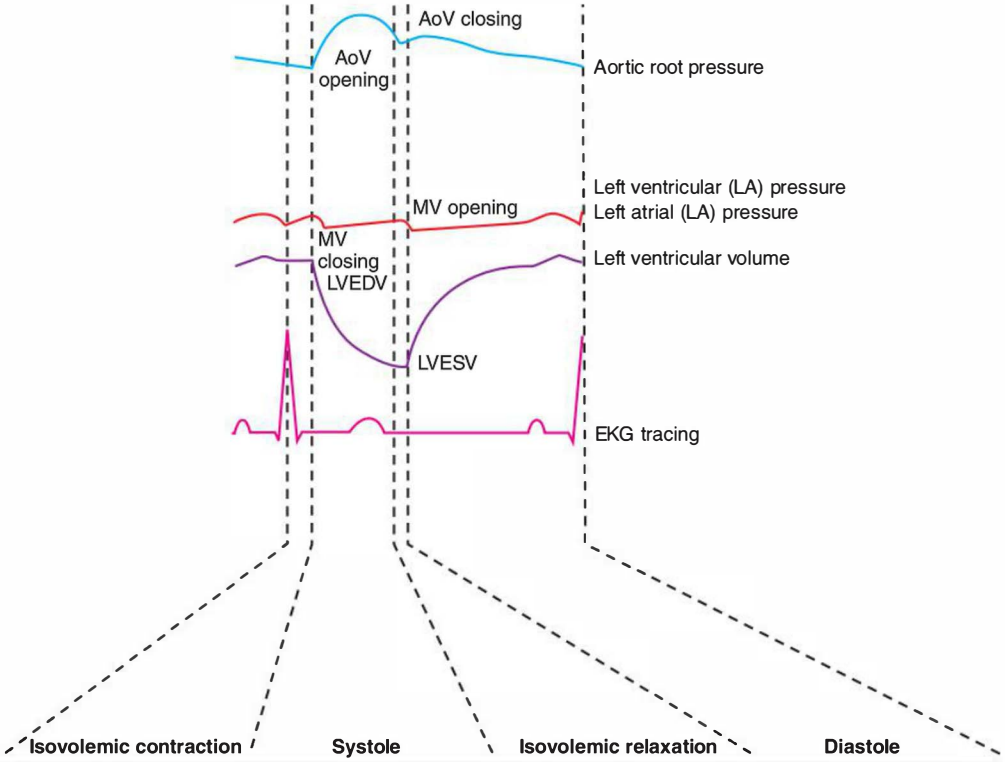
***Normal Mitral Valve Function.*** Normal MV function requires the coordinated and proper functioning of all components of the valve structure: the valvular leaflets, the annulus, the chordae tendineae, the PMs, the LV wall, and the left atrium (LA). The complex interaction of these components can be analyzed through division of the cardiac cycle into four periods: systole, diastole, isovolemic relaxation, and isovolemic contraction (Fig. 31-6).

***Ischemia and Mitral Valve Components.*** As was noted above, in IMR, the leaflets and annulus usually function normally. The chordae tendineae are also not affected by ischemia. However, the PMs contain functioning myocardium that is dependent on end-artery perfusion and are thus sensitive to ischemic insult. There are two PMs: the anterolateral and posteromedial PMs. The anterolateral PM often is supplied by two arteries, most often the first circumflex marginal artery and the first diagonal branch of the left anterior descending (LAD) artery.[224] Ischemia is uncommon in this location and in the surrounding high lateral wall of the LV because of the extensive collateral system. In contrast, the posteromedial PM lies in the watershed of the right coronary and circumflex arteries and more often is supplied by only a single artery; it is therefore highly sensitive to ischemic insult.[224–226] Variations in PM anatomy may lead to increased sensitivity to ischemia; in particular, narrow PMs supplied by a single central artery are vulnerable to ischemia.[227]

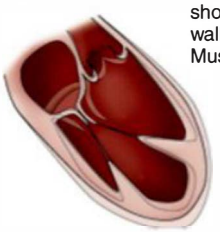
IMR occurs most commonly in association with transmural posteroinferior infarctions.[207,228,229] The location and size of the infarct influence the occurrence and acuity of MR after MI. In a sheep model, ligation of the two most distal circumflex arteries resulted in 21 percent LV mass infarct and gradual development of MR over 8 weeks, ligating the posterior descending artery (PDA) as well increased infarct size to 32 percent and led to immediate MR.[229,230] Similar-sized infarcts in other portions of the heart did not lead to MR.[231]

## Pathophysiology

IMR can be classified broadly into three categories: (1) PM rupture, (2) acute MR, and (3) chronic MR. These conditions result in a variety of disorders of MV function. Carpentier functional categorization of MV dysfunction has been applied




| | Isovolemic contraction | Systole | Isovolemic relaxation | Diastole |
|---|---|---|---|---|
| **Left artium** | LA filling begins after closure of MV | LA rapidly fills, reaching maximum volume near end-systole | LA begins to empty when LA pressure exceeds LV pressure | |
| **Left ventricle** | LA wall thickness increases | LV twists counterclockwise (as viewed from apex)<br>Peak wall thickness occurs near end-systole | LV reverses complex deformation of systole relaxes and dilates LV wall thickness decreases | LV may generate negative pressure |
| **Valve annulus** | | Valve annulus descends 1 to 1.5 cm toward apex<br>Asymmetric contraction of the annulus occurs with minimal valve area near mid-systole | Area of valve annulus increases slightly | Annulus ascends (away from apex) during late diastole |
| **Mitral leaflets** | Flow through the valve briefly reverses with coaptation of the mitral leaflets and bulging into the atrium | | Leaflets separate approximately 30 msec prior to the point where LA pressure exceeds LV pressure | Mitral orifice becomes maximal just prior to onset of atrial contraction<br>Peak blood flow occurs early in diastole prior to maximal valve orifice |
| **Chordae tendinae** | | | Chordal tension decreases rapidly | Chordal tension remains approximately zero until late distole |
| **Papillary muscles** | Papillary muscles begin to shorten | Papillary muscles contract in synchrony with shortening of adjacent LV wall<br>Muscles shorten 2–4 mm | Papillary muscles shorten slightly | Papillary muscles lengthen |



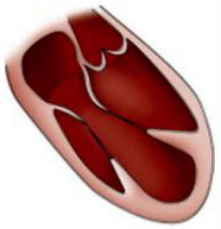


**FIGURE 31-6** Normal mitral valve function requires the coordinated motion of all components of the mitral valve apparatus, including the atrial and ventricular walls. LV, left ventricular; MV, mitral valve; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; EKG, electrocardiogram.

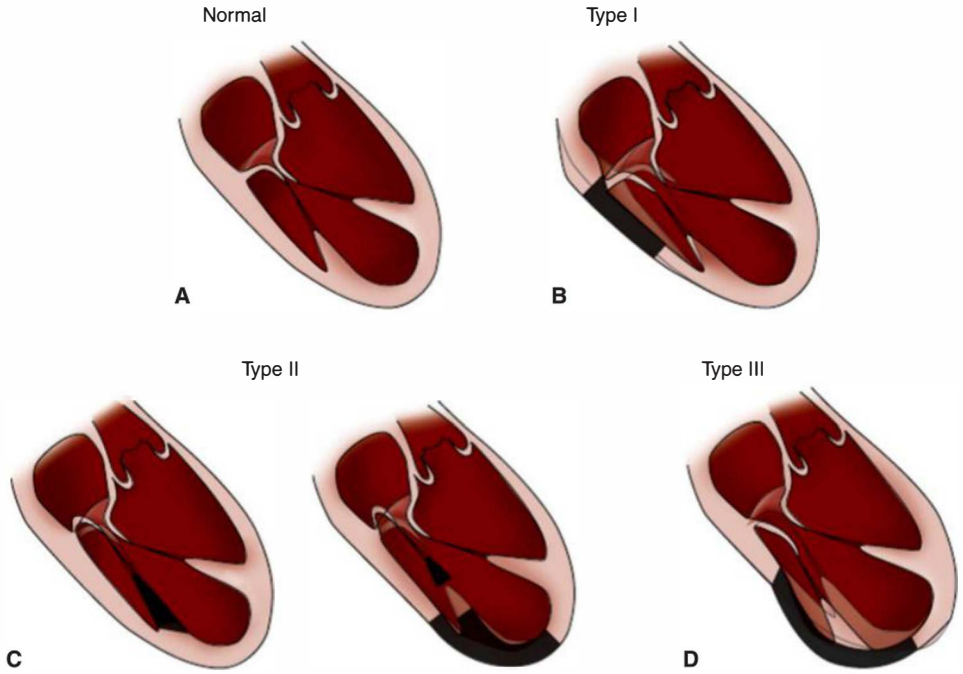



**FIGURE 31-7** Classification of ischemic mitral regurgitation with diagrams of systolic function. **A.** Normal valve function with coaptation of mitral leaflets during systole. **B.** Type I: normal leaflet motion, regurgitation resulting from annular dilatation from ischemia of the adjacent ventricular wall. This results in a central leak. **C.** Type II: prolapsing leaflets. Regurgitation results from either papillary muscle rupture (*left*) in the acute setting or papillary muscle elongation (*right*) secondary to chronic ischemia. This usually results in an asymmetric leak. **D.** Type III: restricted leaflet motion resulting from dysfunction of the ventricular wall and papillary muscle tethering. Type III dysfunction can be sub-categorized as type IIIa and IIIb, depending if there is restricted leaflet opening or closure. This may result in either a central or an asymmetric leak, depending on the nature of the ventricular dysfunction.

to the ischemic MV to guide operative management (Fig. 31-7). In this system, MR is categorized by the derangement in leaflet function: valve dysfunction with normal leaflet motion (type I); excess leaflet motion (prolapsing leaflets) (type II); and restricted leaflet motion during valve opening (type IIIa), or restricted leaflet motion during valve closure) (type IIIb). In the setting of IMR, type I dysfunction occurs when ischemia leads to dilatation of the posterior muscular portion of the valve annulus; this type of deformation may occur with either acute or chronic MR. Type II dysfunction results from PM rupture in the acute setting or may result from chronic ischemia that leads to PM elongation. Type IIIa restricted leaflet opening occurs in the setting of chordal or commissural thickening or fusion; type IIIb restricted leaflet closure occurs in the setting of calcification with ventricular aneurysm or dilatation.

## PAPILLARY MUSCLE RUPTURE

Rupture of PMs results in a loss of leaflet tethering, leading to flail mitral leaflets and MR (Carpentier type II). The more commonly affected posteromedial PM consists of one or two large common trunks and multple heads, all of which give off chordae tendineae to both the anterior and the posterior leaflets of the MV. Acute complete rupture of the common trunk leads to massive MR and hemodynamic collapse. In contrast, partial rupture of the common trunk or rupture of one of the heads may lead to more moderate (and better tolerated) regurgitation.[232] However, partial rupture may progress to complete rupture, leading to subsequent acute decompensation.[233,234]

## ACUTE MITRAL REGURGITATION

When not associated with PM rupture, acute MR results from discoordination of the MV complex. Traditionally, it was thought that PM dysfunction, which is caused by poor systolic shortening of the ischemic PM, leads to MV prolapse and regurgitation in the acute setting. However, studies have not demonstrated MV prolapse in acute IMR.[235,236] Loss of PM systolic shortening alone does not account for the MR seen after MI. Rather, dysfunction of the LV wall resulting from myocardial ischemia with hibernation or stunning or from infarction may lead to failure of valve coaptation. Depending on the location of the infarct, this may result primarily from annular dilatation (Carpentier type I), as was demonstrated by Miller's group, among others,[207,237,238] or by changes in the interaction between the ischemic and nonischemic PMs during systolic contraction, leading to PM tethering and restricted leaflet motion (Carpentier type IIIb).[230,239,240] When not repaired in the acute phase, MR unrelated to PM rupture may disappear, remain unchanged, or become more severe.[241]

### CHRONIC MITRAL REGURGITATION

Chronic IMR also results from a complex of abnormalities in the valvular apparatus. However, in constrast to acute MR, in which changes may be small and difficult to visualize with current imaging techniques, chronic MR usually results in larger changes that are easily apparent on echocardiography. Although some authors have described lengthening of the PM resulting in MV prolapse (Carpentier type II),[206,242] pathologic studies suggest that PM atrophy and scarring are more common.[229,235,243] This results in leaflet tethering during systole, preventing proper coaptation. This phenomenon has been observed in animal models.[244] LV remodeling in general and dilatation in particular (resulting in both dislocation of the PM apically and laterally and dilatation of the valve annulus) further contribute to leaflet tethering through apical displacement of the PM during systole.[245–249] Three-dimensional (3-D) modeling of changes in MV and ventricular function demonstrates that all these changes—posterior PM displacement, annular dilatation, and apical restriction of the posterior leaflet—are associated with the development of IMR (Fig. 31-8).

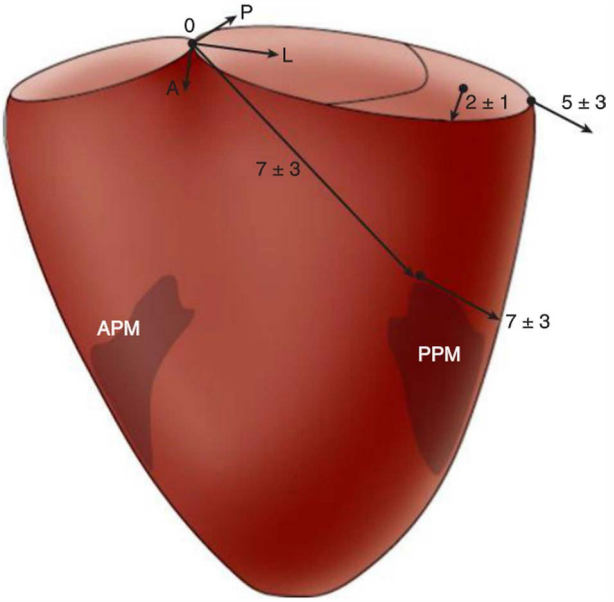



**FIGURE 31-8** Comparison of ischemic changes in mitral valve geometry with and without mitral regurgitation in an ovine model. Arrows represent changes from baseline in the group of animals developing mitral regurgitation that were significantly different from changes occurring in animals that did not develop regurgitation despite similarly located and sized infarcts. Animals developing ischemic mitral regurgitation had more severe displacement of the posterior papillary muscle, septal–lateral dilatation of the annulus, and apical tethering of the posterior leaflet. APM, anterior papillary muscle; PPM, posterior papillary muscle. (From Tibayan FA, Rodriguez F, Zasio MK, et al. Geometric distortions of the mitral valvular-ventricular complex in chronic ischemic mitral regurgitation. *Circulation* 2003;108(Suppl 1):116–121.)

Ideally, operative therapy should be directed toward the causes of MR in each patient. When tethering and apical displacement are responsible for poor leaflet coaptation (Carpentier type IIIb), lengthening of the PM theoretically should ameliorate MR by displacing the attachment points of the chordae toward the valve. In contrast, when annular dilatation is the primary abnormality (Carpentier type I), MV repair with a ring annuloplasty is the most appropriate surgical option.

### EPISODIC ISCHEMIC MITRAL REGURGITATION

A small but important subset of patients may present with chronic *episodic* MR. Patients with this entity develop episodes of dyspnea or flash pulmonary edema with or without associated angina.[250] The murmur of MR will appear during these episodes and subsequently resolve during asymptomatic periods.[251] In these patients, MR is an anginal equivalent caused by transient ischemic dyskinesia of the LV wall that results in apical displacement of the mitral leaflets (Carpentier type IIIb).[252] Because the regurgitation is caused by ischemia of the ventricular wall, treatment should be directed toward ischemia rather than MV function; revascularization without MV surgery should be performed.

## Clinical Features

### PAPILLARY MUSCLE RUPTURE

PM rupture usually leads to acute and rapid hemodynamic collapse with massive MR. Severe pulmonary edema is almost invariably present. It occurs a median of 1 day (and nearly invariably within 14 days) after the onset of infarction.[253] The murmur of MR (a holosystolic murmur best heard over the apex) may be mild or absent. This probably is due to three factors: (1) The wide regurgitant orifice causes a minimum of turbulence; (2) the pressure gradient between the LA and the LV normalizes rapidly, reducing turbulence, and (3) the auscultatory findings of severe pulmonary edema may mask the murmur entirely.[254–256] PM rupture is a rare (occurring in 0.3 to 5 percent of patients with acute MI)[233,257,258] but devastating complication of MI. Mortality rises rapidly in patients with PM rupture: 50 percent at 24 h and 75 percent at 48 h.[233] Median survival in medically managed patients ranges from 1 to 4 days in various series.[233,234]

### ACUTE AND CHRONIC MITRAL REGURGITATION

Depending on the severity of MR that occurs in association with MI, the presentation may range from a new murmur to severe pulmonary edema. Patients who present with mild asymptomatic MR acutely after an MI may be managed as if the MR were not present. When it is not related to PM rupture, acute MR becomes apparent a median of 7 days after infarction.[234,253] However, a subset of patients (approximately 0.1 percent of those with symptomatic coronary disease) will develop acute severe MR.[259] These patients invariably

require surgery for survival. Patients present with symptoms of acute coronary syndromes, including acute onset of chest pain and/or shortness of breath. Pulmonary edema, systemic hypotension, and ultimately cardiogenic shock may ensue rapidly.

As was noted above, infarct size may affect the acuity of the presentation, with chronic MR resulting from smaller LV infarcts. Unlike organic MR,[260] the murmur of IMR correlates poorly with the severity of the regurgitant volume, partly as a result of the low flow present in an ischemic heart.[261] In addition, as many of 50 percent of patients with moderate or severe MR may be missed on physical examination alone.[214] Therefore, even low-intensity murmurs in patients who present with acute MI should be investigated to rule out MV pathology, especially in patients in whom cardiogenic shock or pulmonary edema is associated with well-preserved LV function.[254,261]

The literature on chronic IMR is confounded by the inclusion of patients with nonischemic organic mitral disease in most large series. However, patients with MR appear to have more severe CHF and are more likely to have renal failure than are those without MR.[262] Data from the Cleveland Clinic excluded patients with nonischemic MR. Of the 482 patients undergoing isolated MV surgery for IMR, 80 percent had chronic MV disease. Although separate analyses were not performed for that population, heart failure was common, with 32, 30, and 36 percent of patients in New York Heart Association (NYHA) class II, III, and IV functional status, respectively.[228]

Overall, MR is found in 15 to 20 percent of patients after MI.[214,216] Multiple investigators have demonstrated the association between MR in the setting of acute MI and poor outcomes.[213,263] Barzilai and associates showed a two-fold increase in mortality (36 vs 15 percent), but that difference disappeared when it was controlled for comorbid conditions.[263] More recent studies, however, though confirming the association between MR and multiple predictors of poor outcomes (including older age, multivessel disease, and severe LV dysfunction),[214,216] have shown an independent effect of MR on cardiovascular mortality. In the 727 patients involved in the Survival and Ventricular Enlargement (SAVE) study, the presence of mild or moderate MR was associated with a two-fold increase in cardiovascular mortality in multivariate analysis (median follow-up 3.5 years).[216] Tcheng and colleagues found a similar effect at 1 year (odds ratio 1.5) in patients with moderate or severe MR.[214] Grigioni and associates found that the degree of MR [as measured by estimated regurgitant orifice (ERO)] correlated with mortality in a population of 303 patients operated on more than 16 days after MI with either mitral repair or replacement (risk ratio for ERO less than 20 $mm^2$ 1.65; for ERO equal to or greater than 20 $mm^2$ 2.23).[264] Similar results were seen in a series of 4221 patients undergoing PCIs remote from an MI; the 53 patients with moderate or severe MR had 3-year survival of 68.6 vs 92.3 percent for those without any MR.[262] This difference was even more pronounced among those with a LVEF less than 40 percent. Similarly, in the SHOCK trial, both severe MR and depressed LVEF were predictors of increased 1-year mortality regardless of treatment assignment.[26]

In summary, ischemic MV disease consists of a spectrum of clinical presentations that ranges from acute to chronic and from mild to severe. However, it is associated with poor outcomes regardless of severity.

## Diagnostic Modalities

### ECHOCARDIOGRAPHY

Echocardiography provides useful diagnostic and prognostic information in both acute and chronic MR. Acutely, transthoracic echocardiography (TTE) is the diagnostic study of choice in evaluating patients with hemodynamic instability after MI. TTE enables the detection of wall motion abnormalities, quantitation of the degree of MR, and assessment for other mechanical causes of circulatory collapse, including septal or free wall rupture; it also may demonstrate flail mitral leaflets or other evidence of PM rupture. The preoperative TTE should be used in planning intervention on the MV as intraoperative transesophageal echocardiography (TEE) often underestimates the amount of regurgitation.[265]

When TTE does not provide adequate information about PM integrety, TEE may be required; some authors recommend routine TEE because of the failure of TTE to detect MR and PM rupture in up to 80 percent of patients.[257] Because of the high mortality rate associated with PM rupture without operation, detection of this uncommon complication as part of the evaluation of patients with MI is imperative. Traditionally, PM rupture was identified by locating a mobile mass attached to the mitral leaflet prolapsing into the right atrium; however, even with TEE this may fail to detect PM rupture in as many as 35 percent of patients; a complete evaluation of the LV is also necessary to evaluate for large-amplitude erratic motion of the PM head in the LV that is indicative of rupture (Fig. 31-9).[226]

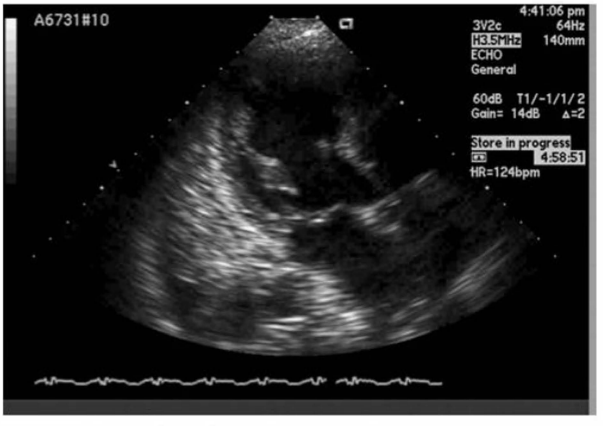



**FIGURE 31-9** Echocardiography of mitral regurgitation caused by papillary muscle rupture with mobile mass attached to the mitral leaflet.

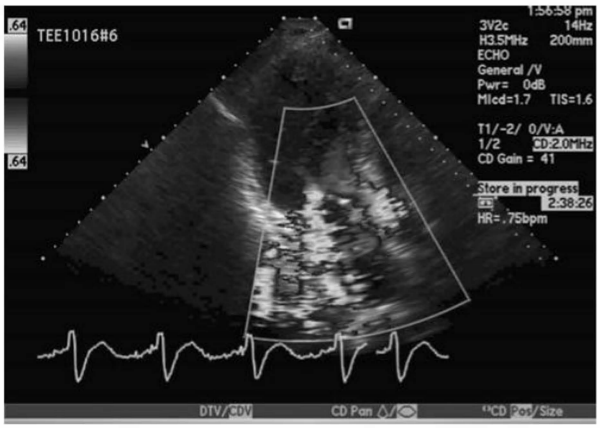



**FIGURE 31-10** Echocardiography of mitral regurgitation demonstrating regurgitant jet using Doppler imaging.

In chronic MR, echocardiography can be used to follow progression of disease as well as distinguish ischemic from organic pathology. Doppler echocardiography allows identification and quantification of mitral regurgitant flow (Fig. 31-10), and two-dimensional echocardiography can be used to examine LV structure and identify abnormalities in leaflet and chordal morphology and function. TEE is superior to TTE in the evaluation of valvular pathology, particularly in identifying sequelae of endocarditis such as vegetations, leaflet perforations, and inflammatory changes.

### ANGIOGRAPHY

The increased diagnostic accuracy of echocardiography has allowed it to replace angiography in the assessment of MR. Thus, angiography remains clinically useful primarily in delineating coronary anatomy and treating stenotic lesions when appropriate. Despite hemodynamic instability, most patients who present with MR in association with acute MI will receive an angiogram.

In chronic MR patients, a preoperative angiogram also is used to delineate coronary anatomy and plan the operative procedure and approach. Measurement of intracardiac and intravascular pressures as well as cardiac output assists in the assessment of LV function. However, in light of the high incidence of renal failure in this population,[228] a ventriculogram should be avoided because it provides little information beyond that obtainable by echocardiography.

## Medical Therapy

### ACUTE MITRAL REGURGITATION

Therapies directed at patients with acute MR after MI depend largely on the degree of regurgitation and the patient's hemodynamic status. In most patients, the presence of MR will not affect the management of acute infarction; however, a minority of patients will develop 3+ or 4+ MR with heart failure and cardiogenic shock. These patients with acute severe MR should be admitted to the intensive care unit (ICU) until definitive therapy (surgery or, catheter-based interventions) can be instituted.

Diagnostic studies should be initiated to determine the cause of the decompensation; patients with PM rupture in particular must receive rapid operative therapy. In the ICU, patients should have advanced cardiac monitoring. Fluid resuscitation should be directed by measurements of cardiac filling as both hypovolemia and volume overload may impair cardiac function significantly. Patients in cardiogenic shock may require inotropic therapy and, when inotropic therapy is inadequate, an IABP may be helpful. In the setting of MR, an IABP has been shown to decrease the regurgitant fraction and increase systemic cardiac output and carotid blood flow, all without changing LV function.[266]

Telemetry monitoring should be used to assess for arrhythmias, which are common in postinfarction MR. The antiarrhythmic agents used should be those least likely to cause hypotension or impair myocardial contractility. Electrical cardioversion may be the best choice for patients with tachyarrhythmias, and transcutaneous or transjugular pacing may be required to control bradyarrhythmias in this setting.

### CHRONIC MITRAL REGURGITATION

A variety of pharmacologic agents are available for treating patients with chronic MR. Vasodilators and ACE inhibitors or angiotensin-1 (AT1) receptor blockers improve LV volume and decrease the regurgitant fraction through a reduction in afterload. However, no trial has demonstrated an improvement in survival with these treatments. In patients with LV systolic dysfunction, β-blockers have a positive effect on ventricular remodeling and the ejection fraction and have been shown to reduce the volume of MR. Combined use of vasodilators and β-blockade may be particularly useful in patients with MR and LV dysfunction.

## Surgical Therapy

### OPERATIVE INDICATIONS

***Papillary Muscle Rupture.*** Surgery is the only effective therapy for PM rupture. Although mortality rates are high,[267,268] the rates for nonoperative management are higher. Depending on the location of the rupture, different operative techniques may be indicated. In the setting of PM trunk rupture, MV replacement is recommended. When rupture of the PM head occurs but the adjacent head and body remain viable, repair of the PM may be an option. However, these repairs should be attempted only when the patient's clinical condition allows. Commonly, PM rupture combined with ongoing cardiac motion leads to entanglement of the muscle within the other chordal structures; complete disentangling must be performed before repair to preserve ventricular and valvular function.[269] When the clinical situation

does not allow for repair of the PM, MV replacement should be performed.

***Acute Mitral Regurgitation.*** Most patients with acute MR after MI are managed with medical therapy and PCI. However, in addition to those with PM rupture, at least four subsets of patients may require operative therapy in the acute setting: (1) patients with coronary artery disease requiring surgical revascularization, (2) patients with acute postinfarct angina, (3) patients with acute postinfarction angina and 1+ to 2+ MR, and (4) those with acute severe MR in association with progressive heart failure and cardiogenic shock.

Patients in whom percutaneous intervention does not achieve adequate revascularization and those with important left main or severe three-vessel coronary artery disease require surgical intervention. Revascularization should be performed first in this population; if postbypass echocardiography continues to demonstrate significant (2+ or greater) MR, valve repair or replacement should be performed.

Individuals with postinfarct angina should be managed initially with emergent medical or percutaneous revascularization to relieve angina and prevent extension of the infarct, which might result in heart failure, worsening MR, and cardiogenic shock. Although CABG rarely is completed in time to prevent reinfarction in patients with postinfarct angina, it may decrease eventual infarct size.[270–272] In these patients, exposure of the MV should not be performed unless intraoperative TEE demonstrates 3+ or 4+ MR.

Patients with acute severe MR with hemodynamic instability require emergent revascularization, usually surgical. Although there have been reports of resolution of MR with thrombolysis alone, the results have been inconsistent.[214,217,273,274] Rapid (within 4 h of symptom onset) percutaneous revascularization also has demonstrated occasional dramatic resolution of severe MR in settings where viable myocardium remains in the distribution of the culprit artery.[214,274,275] However, even with successful medical or percutaneous revascularization, mortality rates remain high, and most of these patients continue to have 3+ to 4+ MR.[276]

Indications for operative management of acute severe MR vary between institutions but include pulmonary edema, LV failure, and failure of nonsurgical revascularization to abolish MR; the urgency of MV management depends on the presence or absence of cardiogenic shock.[276] In these patients, medical therapy alone has nearly universal mortality.[234,277,278] Operation for acute severe MR should consist of valve repair or replacement with or without myocardial revascularization.

Both mitral valve repair (MVr) and mitral valve replacement (MVR) are options in these patients. Although long-term results appear to be similar within matched cohorts,[228,279] patients undergoing repair for acute severe MR have higher reoperation rates as a result of valve failure.[279] The difficulty of assessing the viability and long-term strength of the valvular apparatus may play a role in these failure rates. During replacement, whether mechanical or biological prosthetic valves are chosen, it is important to preserve chordal attachments to preserve LV geometry.[280]

Bypass grafts should be placed to revascularize all significantly obstructed coronary vessels that are remote from the infarct. Although the survival benefit of revascularization of the infarct-related artery after more than 4 to 6 h of symptoms is not clear, even in completed infarctions revascularization appears to improve LV remodeling.[271,272,281] In contrast, blind revascularization of coronary arteries in patients without preoperative angiograms is not likely to be of benefit: Fewer than 50 percent of patients with acute severe MR have multivessel disease,[277,282] and a prolonged operation may increase mortality further in this critically ill population.

***Chronic Mitral Regurgitation.*** Patients with chronic MR after MI form the largest group of patients who require MV surgery for ischemia. Patients who require surgical revascularization may have MR that ranges from mild to severe with a corresponding range of symptoms (Fig. 31-11).[283] At the ends of this spectrum, management of patients is relatively clear. In those with only trace or mild MR and few symptoms of heart failure, CABG alone should be performed; in

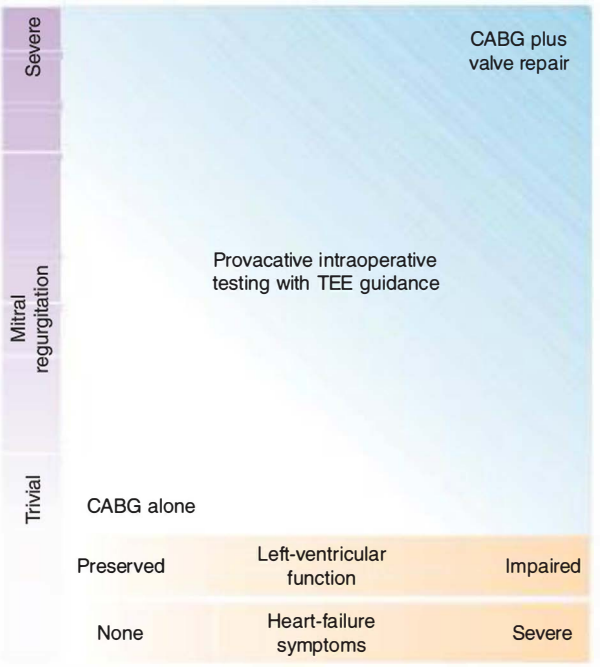



**FIGURE 31-11** Diagram of operative management of chronic mitral regurgitation. Patients with minimal mitral regurgitation and good ventricular function should be managed with CABG alone; those with severe ventricular dysfuction and severe MR warrant mitral valve surgery. Management of patients falling in the intermediate area remains controversial. CABG, coronary artery bypass grafting; MR, mitral regurgitation. (From Byrne JG, Aklog L, Adams DH. Assessment and management of functional or ischaemic mitral regurgitation. *Lancet* 2000;355(9217):1743–1744.)

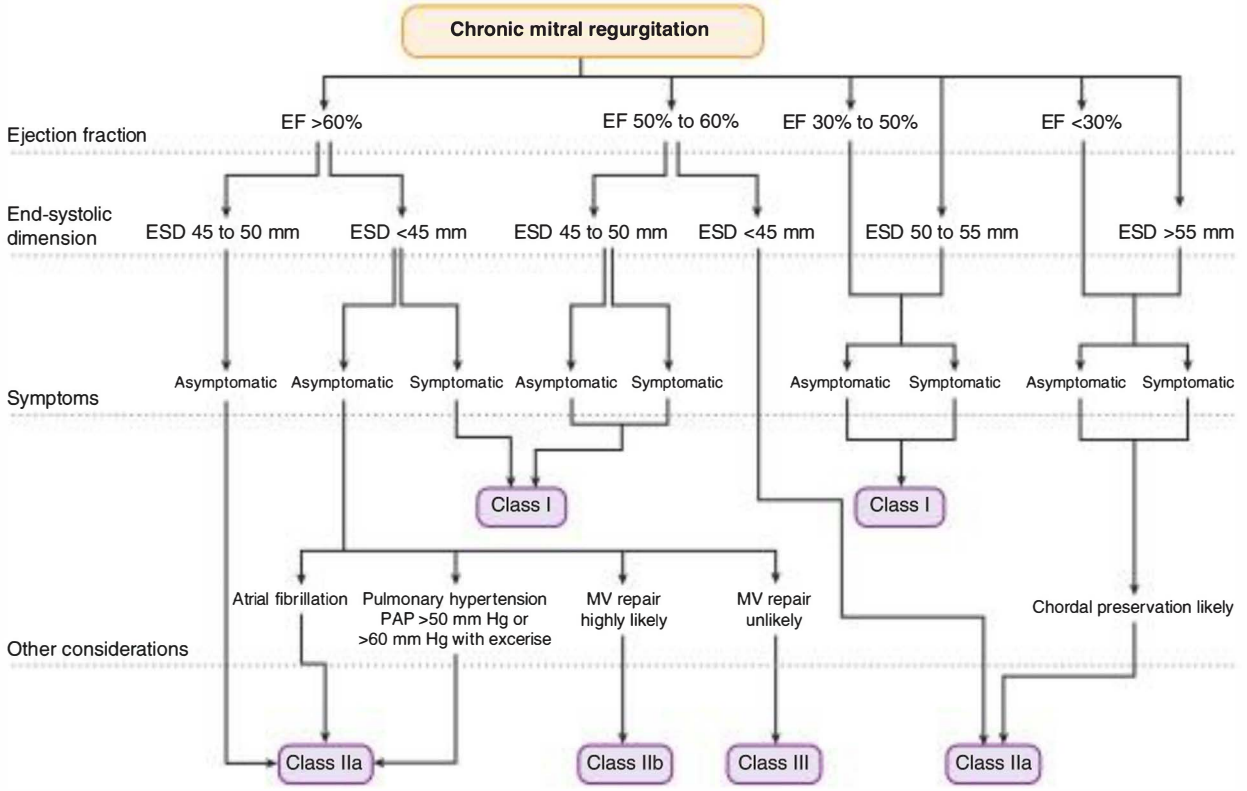



**FIGURE 31-12** Flowchart indicating recommended management of chronic nonischemic mitral regurgitation or chronic ischemic mitral regurgitation without viable myocardium for reperfusion therapy. Class I, evidence and/or agreement that surgery is useful and effective; class IIa, divergence of opinion: weight of evidence/opinion favors usefulness; class IIb, divergence of opinion: usefulness less well established; class III, not indicated or harmful. [Based on the recommendations of the American College of Cardiology/American Heart Association as published in Bonow RO, Carabello B, de Leon AC, et al. ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease: Executive Summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *J Heart Valve Dis* 1998;7(6):672–707.]

those with severe (3+ to 4+) MR and significant sequelae, concomitant MV surgery is indicated.

Management of patients in the middle of this spectrum remains controversial, with few data to guide therapy. Some series suggest that long-term outcomes in these patients are equivalent whether CABG or CABG with MV surgery is performed.[284] However, CABG alone does not treat MR,[285] and MR even of only mild or moderate severity has been associated with increased long-term mortality.[216,264] Intraoperative assessment of MV function in these patients should include preload and afterload challenges to mitigate the unloading effects of general anesthesia.[205,228,286,287] If provocative testing fails to unmask significant (3+ or 4+) MR or if the resultant MR is associated with focal wall motion abnormalities from the development of ischemia, CABG can be performed without inspection of the MV. However, if these tests demonstrate regurgitation, MV repair or replacement should be considered.

Some patients with IMR may not have viable myocardium that is amenable to surgical revascularization. In these patients, indications for surgical intervention are the same as those for patients with functional nonischemic regurgitation (Fig. 31-12). In contrast to patients undergoing concomitant CABG and valve surgery, in this population the increased afterload after MV surgery is not balanced by improved ventricular function after revascularization; therefore, operative intervention may be poorly tolerated, and many patients may go on to require heart transplantation.

## PERIOPERATIVE CONSIDERATIONS

***Acute Severe Mitral Regurgitation.*** Overall surgical management of these patients is similar to the management of those with cardiogenic shock in the absence of MR (see above). CPB should be initiated via direct cannulation of the ascending aorta and bicaval cannulation via the right atrium. Bicaval cannulation maintains decompression during the mitral repair, particularly when exposure of the MV causes superior vena caval obstruction. After aortic cross-clamping and myocardial protection via retrograde and antegrade cardioplegia, the LA is opened. The distal coronary arteries

should be grafted before valve surgery. It is important to ensure that all grafts are secure before beginning the valve surgery, as it may be difficult or dangerous to retract the heart after implantation of the prosthetic ring or valve because of the risk of dehiscence or LV rupture.

***Chronic Mitral Regurgitation.*** Preoperative preparation in these patients is similar to that for other cardiac operations. The surgical approach and the institution of CPB are the same as those described for acute MR and include bicaval cannulation, the use of retrograde and antegrade cardioplegia, and the construction of arterial grafts before the valve procedure. After the induction of anesthesia, the MV should be assessed carefully with TEE to evaluate whether valve surgery is required; if doubt exists, provocative testing should be performed after placement of the arterial cannula.

## OPERATIVE TECHNIQUE

***Repair of Rupture of the Papillary Muscle Head.*** Double-armed, pledgeted 4-0 polypropylene sutures are passed through the viable PM trunk and then into the PM head, where another pledget is used to buttress the knot (Fig. 31-13). The addition of gelatin-resorcinol-formalin glue may help strengthen the repair.[276] In the case of avulsion of the primary chordae, chordal transfer may be performed with a segment of posterior chord. Alternatively, new artificial chordae constructed from extended polytetrafluoroethylene (ePTFE) sutures may be used.[288]

***Mitral Valve Repair vs Replacement.*** The use of repair vs replacement in IMR remains controversial. Because randomized studies are not available to answer this question, large retrospective cohorts provide the only guidance. Gillinov and associates recommend valve repair in most patients. Among the low-risk matched cohorts, MVr had a trend toward improved short- and long-term survival (30-day, 1-year, and 5-year survival 94, 82, and 58 percent vs 81, 56, and 36 percent).[228] However, in the high-risk group, outcomes were similar.[228] When MVr was performed, outcomes were improved with the use of internal thoracic artery graft and the use of a formal annuloplasty band or ring (rather than a pericardial strip).[228] Grossi and associates reported similar results with repair.[279] Patients who may benefit from replacement rather than repair include elderly patients with severe LV dysfunction who may not tolerate a prolonged operation[276] and patients with severe ventricular and PM dysfunction that causes significant type III regurgitation. In these patients, repair may not lead to functional coaptation of the mitral leaflets.[228,261,279] Most authors strongly favor repair in the majority of patients with IMR, citing over 90 percent freedom from operation.[289] In examining over 3,000 patients, Galloway et al. report 93 ± 1 percent freedom from reoperation at 8 years for minimally invasive MVr.[290] Whichever surgical treatment is preferred, careful inspection of the valve should be performed after cardiotomy to identify abnormalities in the PMs and chordae as well as defective leaflet tissue to direct appropriate therapy.



**FIGURE 31-13** Illustration of reimplantation of the ruptured papillary muscle head onto the trunk of the viable adjacent papillary muscle. (Adapted from Fig. 32-8 in Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 1998.)

***Chordal-Sparing Mitral Valve Replacement.*** Chordal sparing techniques should be used for valve replacement in all patients with IMR. This can be performed by securing the chordae to the valve annulus as described by Khonsari and colleagues (Fig. 31-14).[276] This technique permits resuspension of the chordae with preservation of subvalvular anatomy while allowing for sufficient resection of the anterior leaflet to avoid obstruction of the left ventricular outflow tract (LVOT). The anterior leaflet is excised, and the rim of leaflet containing the chordal attachment is reattached to the anterior annulus with pledgeted sutures (Khonsari I) (Fig. 31-14A). When the leaflet is calcified, it may be necessary to subdivide the leaflet into two to four segments and reattach each segment to the annulus in an anatomic fashion. If the anterior leaflet is soft and pliable, a central ellipse may be excised and the leaflet free edge may be reattached to the annulus (Khonsari II) (Fig. 31-14B). The posterior leaflet can simply be plicated using horizontal mattress sutures to secure the chordal-leaflet junction to the posterior annulus. The stitches should be placed through the chordal-leaflet junction to elevate the chordae to the level of the valve and preserve the chordal contribution to normal LV geometry as much as possible (Fig. 31-14C).

The decision to use bioprosthetic or mechanical valves should be individualized to the patient on the basis of life expectancy and the risks of anticoagulation. Patients at high risk for anticoagulation or with a life expectancy less than 5 or 6 years are candidates for bioprosthetic valves at most centers.

***Mitral Valve Repair.*** A wide variety of techniques for MVr have been reported; however, 98 percent of patients in the

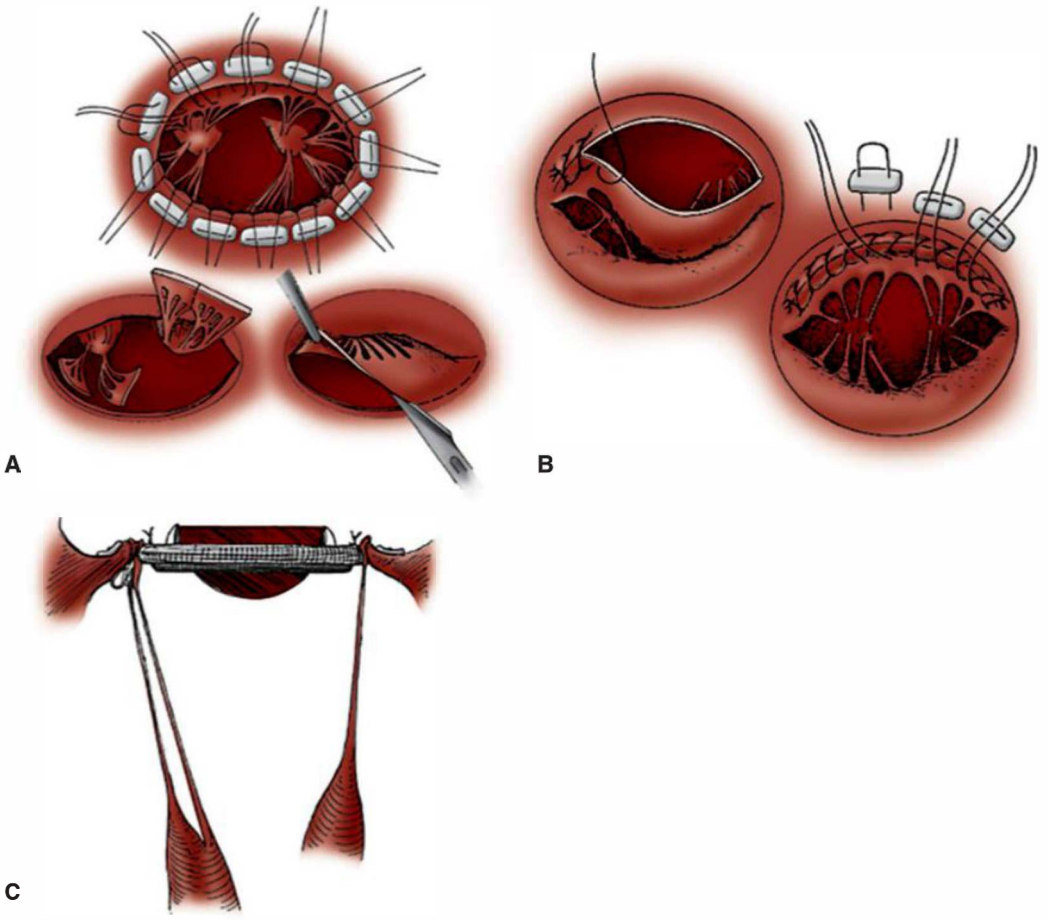



**FIGURE 31-14** Illustration of techniques for chordal preservation during mitral valve replacement. **A.** Khonsari I technique. The anterior leaflet is excised from the annulus while preserving the leaflet–chordal junction. The leaflet then is divided if necessary, and the chordae are resuspended in their normal anatomic positions surrounding the annulus. **B.** Khonsari II technique. When the valve leaflet is soft and pliable (as is common in ischemic mitral regurgitation), a central ellipse of the anterior leaflet is excised, and the free edge is reattached to the annulus, using the valve sutures. **C.** Cross-sectional image. The relationship of the excised anterior leaflet and plicated posterior leaflet to the valve structure is clearly indicated. (Adapted from Fig. 34-10 through 34-12 in Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 1998.)

study by Gillinov and associates[291] underwent annuloplasty, and this is the most common and most consistently effective method. Sizing of the valve should be performed as with standard MV surgery, using the intertrigonal distance and the area of the anterior leaflet; an undersized annuloplasty is generally preferred. In the Gillinov series, 79 percent of patients had annuloplasties of less than 30 mm, and other series have reported excellent results using undersized annuloplasty for MVr.[228,286,287] Both complete annuloplasty rings and posterior annuloplasty bands have been used, and the results appear similar.[228] However, the additional time required for insertion of a complete ring argues against their continued use.

The annuloplasty ring is sutured into place with 2-0 Dacron horizontal mattress sutures from the left fibrous trigone to the right fibrous trigone along the LV free wall (Fig. 31-15).[276] The sutures should be spaced so that the medial 50 percent of sutures are placed into only 40 percent of the circumference of the annuloplasty ring; this plicates the medial aspect of the annulus and enhances leaflet coaptation.[276] Suture annuloplasty has been reported to enhance coaptation of the leaflets, as has commissuroplasty. Although suture annuloplasty is simple and rapid, the long-term results are poor. Commissuroplasty has significant disadvantages, including instability, partial dehiscence, and the potential to narrow the MV.[276]

Postrepair intraoperative TEE is essential to the operative management of patients undergoing MVr, and its use is associated with improved long-term outcomes after repair.[291] The degree of MR on intraoperative TEE correlates well with early and late postoperative results.[292,293] Although trace to mild residual MR is frequently present and is not associated

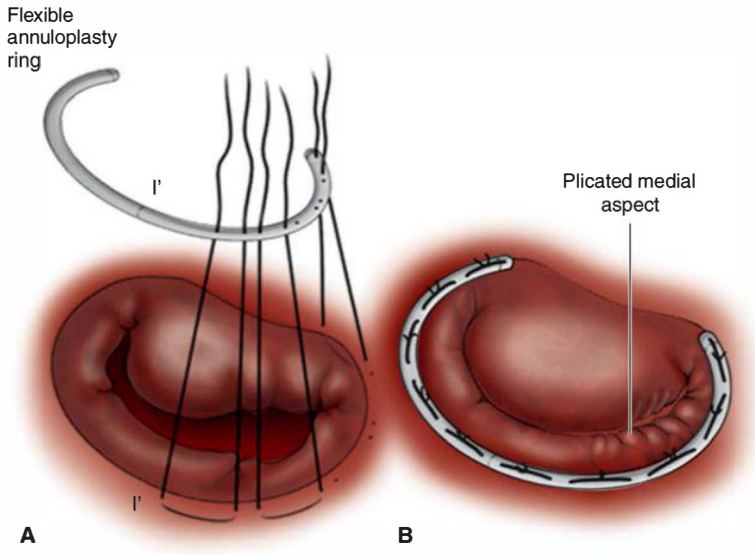



**FIGURE 31-15** Placement of a flexible annuloplasty ring for mitral regurgitation. **A.** The sutures are placed into the annulus in an asymmetric manner so that 50 percent of the sutures along the medial aspect are placed into only 40 percent of the annuloplasty ring. **B.** This results in preferential plication of the region of the posteromedial commissure and enhances coaptation between the anterior and posterior leaflets. (Adapted from Fig. 23.8A and B in Buxton BF, Frazier OH, Westaby S (eds). *Ischemic Heart Disease Surgical Management*. Philadelphia: Mosby, 1999.)

with decreased survival, it portends a higher reoperation rate.[294] Moderate to severe residual regurgitation at discharge is associated with poor long-term survival[295] and, when identified intraoperatively, necessitates a return to CPB and reevaluation of the valve. Redo of the repair has been successful in some populations,[296] but in patients undergoing prolonged procedures with concomitant CABG valve replacement it should not be delayed. In large series, reinstitution of bypass and redo of the valve surgery are required in approximately 2 to 7 percent of cases.[297,298]

In addition to identifying residual MR after repair, TEE is important in detecting dynamic LVOT obstruction caused by systolic anterior motion (SAM) of the anterior mitral leaflet into the LVOT (Fig. 31-16). A variety of factors are associated with the development of SAM after MVr: excessive anterior leaflet tissue, increased posterior leaflet height, a hyperkinetic heart, a prominent interventricular septum, a narrow aortic-mitral angle, too small an annuloplasty ring or inaccurate ring orientation, and extensive quadrangular resection of the posterior leaflet.[299] In general, these factors bring leaflet coaptation and the anterior leaflet closer to the septum, resulting in LVOT obstruction. In early series, SAM occurred in approximately 5 to 10 percent of cases of MVr.[300,301] Improvements in operative technique (including the sliding leaflet technique of Carpentier[302,303]) have reduced this incidence in more recent series secondary to reduction in the height of the posterior leaflet.

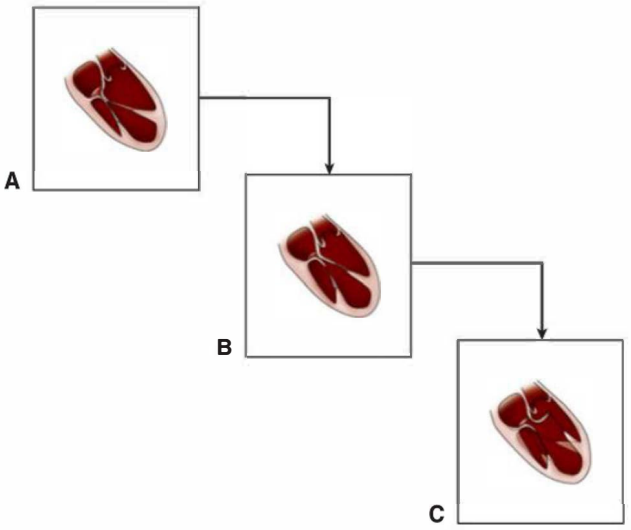



**FIGURE 31-16** Systolic anterior motion of the anterior mitral leaflet and left ventricular outflow tract (LVOT) obstruction. **A.** Normal heart in systole. **B.** Displacement of the anterior mitral leaflet toward the ventricular septum and into the LVOT may be precipitated by the posterior portion of the annuloplasty ring pushing the anterior leaflet too far forward, excessive shortening of chordae or papillary muscles during the operative procedure, left ventricular hypertrophy, or a variety of other factors. **C.** Intermittently, the mitral leaflet may get drawn into the LVOT, causing dynamic obstruction and sudden onset of hypotension.

On TEE, SAM can be seen as protrusion of the free edge of the anterior leaflet into the LVOT. It often is associated with deviation of the coaptation point toward the septum as well as a small left ventricle and a bulging septum.[304] Changes in LV geometry with changes in volume status may play a significant role in the development and presentation of SAM; therefore, not all patients will have abnormal postrepair TEEs. In these patients, the postoperative onset of SAM and LVOT obstruction may be heralded by a rapid onset of hypotension, near syncope, and arrhythmias.[304]

The initial treatment of SAM should be directed at optimization of LV volume to displace the anterior leaflet away from the septum. The use of inotropes should be minimized to reduce hyperdynamic LV contractility. Phenylephrine may be used to increase SVR; the reflex bradycardia increases LV size through an increase in diastolic filling.[299] β-blockade may be useful in increasing diastolic filling as well as treating superimposed tachyarrhythmias.[304] Finally, initiation of AV pacing and adjustment of the pacing intervals have eliminated SAM in some cases.[299] With an appropriate repair, most patients will respond to medical therapy alone,[301] but patients who require large alterations in hemodynamics with phenylephrine and β-blockade should be considered for revision of the MVr or MVR.

***Other Techniques.*** Because annuloplasty and other techniques of MVr do not address the pathology of IMR (which involves dysfunction of the LV wall that leads to failure of leaflet coaptation), attempts have been made to address IMR at the ventricular level. Two techniques have been validated in animal models but have not been evaluated in humans. LV remodeling through plication of the infarct region reduces the distance between the PMs and the mitral annulus; this reduces systolic tenting and decreases the regurgitant volume.[305] A reduction in tenting and an improvement in MR were noted with selective cutting of a limited number of basal chordae tendineae involved in incomplete valve closure.[306] The applicability of these techniques in humans remains to be seen.

Percutaneous valvotomy and valve repair are evolving technologies for use in high risk patients. A number of technologies for percutaneous MV repair are being developed. The best studied is the Evalve MitraClip (Abbott Laboratories, Abbott Park, IL). This system requires a 24F introducer, TEE guidance, and transseptal approach in order to place a clip that will approximate the valve leaflets at the midpoint.[307] This repair technique is based on a type of open repair first described by Ottavio Alfieri, which results in a double oriface MV.[308] Short term outcomes of patients with 3–4+ MR were assessed in the EVEREST prospective multicenter single-arm trial of the MitraClip system. One hundred and seven patients underwent the procedure, 74 percent had immediate improvement of MR, while 64 percent had ≤1+ MR on discharge. Ten patients (9 percent) suffered partial clip detachment, while none had clip embolization. At a mean follow-up of 3.2 years 30 percent of the patients underwent open mitral valve surgery. Kaplan–Meier freedom from death was 95.9, 94.0, and 90.1 percent, and Kaplan–Meier freedom from surgery was 88.5, 83.2, and 76.3 percent at 1, 2, and 3 years, respectively.[309] The EVEREST II study, a multicenter, randomized controlled trial comparing Evalve MitraClip to open surgery demonstrated that the device was significantly less effective at reducing MR than surgery, but the procedure was associated with superior safetly and similar improvements in clinical outcomes. In an associated study the patients that eventually underwent open valve repair were analyzed. Indications for surgery in this group included partial clip detachment ($n = 10$), residual or recurrent MR greater than 2+ ($n = 9$), and other [atrial septal defect ($n = 2$), device malfunction ($n = 1$), and incorrectly diagnosed mitral stenosis ($n = 1$)]. Eighty-seven percent of patients successfully underwent the planned procedure leading the authors to conclude that standard surgical options were preserved in this group of patients.[310] As technology advances and evolves, it is likely indications for percutaneous MV intervention will expand.

## Outcomes and Prognosis

### EARLY RESULTS

Few studies have separately addressed the risks and results of MV surgery for acute MR. Historical series report 30-day mortality rates from 10 to 70 percent,[277,282,311,312] but they do not have significant applicability to contemporary series, and the wide range probably reflects differences in patient selection rather than operative technique. Outcomes have improved, and operative mortality for acute severe MR in most contemporary series (whether limited to PM rupture or inclusive of all types of acute MR) is approximately 20 percent.[313,314] Patients in cardiogenic shock have higher early mortality in all series.[228,278,279,314] Although patient selection may play a role, the 40 percent mortality reported after surgery for acute MR still improves on the 71 percent mortality seen with medical therapy in the SHOCK registry by a wide margin.[313] Early operation in the absence of hemodynamic compromise does not appear to have an effect on operative mortality.[228,279] There is not a clear consensus about the benefits of repair vs replacement in the acute MR population, and large series suggest that the outcomes are probably similar, although many authors continue to recommend replacement in the acute setting.[279,315]

In three large recent reports limited to MV surgery in IMR, operative mortality was 13 percent.[228,279,314] Previous series had a wide spectrum of operative results that ranged from 3.0 to 29.4 percent; this may have been affected by the variable inclusion of patients with chronic non-IMR as well as the heterogeneous population undergoing MR in the setting of coronary artery disease.[205] Similar mortality was observed in the series by Cohn and associates that dealt with patients undergoing concomitant CABG and MVR for IMR.[267] Although multiple studies have demonstrated the

negative impact of concomitant CABG on operative mortality during MV surgery,[314,316–318] this probably reflects the underlying pathology rather than the choice of operative procedure. The large series reported by Grossi and associates[279] and Gillinov and coworkers[228] attempted to control for patient selection in order to compare valve replacement with valve repair. Those authors have initiated an emerging consensus that suggests that valve repair is superior to replacement in this population. Risk factors for early mortality after MV surgery include older age, cardiac dysfunction, complex jet direction (for patients undergoing repair), and severe wall motion abnormalities.[228,279]

### LATE RESULTS

Patients undergoing valve replacement rarely require reoperation for valve failure.[319,320] Although there have been concerns about durability of valve repair for IMR, long-term freedom from repair failure requiring reoperation is excellent: 98 percent at 30 days, 96 percent at 1 year, and 91 percent at 5 years.[228] However, many patients with recurrent MR may not reach reoperation or may not be operative candidates at the time of repair failure. Severe MR may recur in up to 5 percent of patients, and mild-to-moderate MR in 50 percent.[321]

Despite improvements in technique and operative care, only 55 to 60 percent of patients survive 5 years after surgery. In Gillinov's series, among the lowest-risk patients, survival with repair was 58 percent (replacement only, 36 percent), but the highest risk patients had 5-year survival below 50 percent regardless of the procedure performed.[228] Similar results were obtained by Grossi and coworkers.[279] Risk factors for poor outcomes in these groups included poor preoperative cardiac function, previous cardiac surgery, use of suture rather than ring annuloplasty, inferior or lateral wall motion abnormalities, and preoperative atrial fibrillation.[228,279] The poor outcomes probably reflect the impact of large MIs and progressive LV failure on survival and will not be ameliorated by improvements in mitral surgical techniques.

## Summary

There are three forms of IMR: PM rupture, acute MR, and chronic MR. PM rupture requires emergent operative repair, usually with MV replacement, after resection of the ruptured portion. In patients with acute severe MR secondary to ischemia, indications for operation vary between institutions, but emergent revascularization is indicated. When revascularization via thrombolysis or PCI is ineffective, surgical revascularization and MV surgery (usually replacement) are indicated. In patients with chronic MR, MV repair appears to have outcomes equivalent to or better than those of replacement in most populations. Indications for repair include 3+ to 4+ MR in patients needing revascularization. In patients not requiring revascularization, operative decision making is more complex, but in general, symptomatic patients or those with depressed LV function [ejection fraction less than 50 percent or electrostatic discharge (ESD) greater than 50 mm] should be considered for isolated MV procedures. Operative mortality in patients with IMR is approximately 13 percent. Although long-term freedom from reoperation (even with valve repair) exceeds 90 percent at 5 years, survival at 5 years is only 55 to 60 percent. Poor outcomes reflect the impact of large infarctions and extensive coronary disease rather than problems with the mitral surgery.

# VENTRICULAR SEPTAL RUPTURE

## Introduction

First described at autopsy in 1845 by Latham,[322] VSR is a rare but highly lethal complication of MI. The first antemortem diagnosis was not made until 1923,[323] and it would be another 30 years before Cooley and associates[324] performed the first successful repair. Since that time, rapid diagnosis and prompt surgical repair represent the best chance for survival.

Although earlier reports described septal rupture in 1 to 3 percent of cases of MI,[325,326] the advent of reperfusion and aggressive strategies of revascularization have reduced that rate to less than 0.5 percent.[327] However, mortality remains high, and with only 24 percent of medically treated patients (none of them with cardiogenic shock) surviving to 30 days,[328] surgical repair affords an improvement in outcomes, although long-term survivors remain rare.

## Pathophysiology

### PATHOLOGY

VSR occurs after a large transmural infarction when enough necrosis occurs to weaken the septal wall. Infarctions complicated by VSR are larger than those which are not,[329,330] and patients with rupture appear less likely to have diffuse coronary artery disease[328,331,332] (though this has not been found in all reports[333]), to have had previous episodes of angina or MI,[325,332,334–337] and to demonstrate evidence of collateral circulation.[331,334,337] This suggests that large infarctions in myocardial regions that are poorly supplied with collateral perfusion may be at particular risk, but otherwise the reason some hearts rupture and others do not is not clear.

There are two types of VSR: simple and complex (Fig. 31-17). Simple ruptures are discrete lesions with defects at a similar level in both ventricles. The path between the ventricles follows a straight path through the infarcted myocardium. In contrast, complex ruptures have a convoluted dissection path between the ventricles with regions of extensive hemorrhage and may include areas remote from the primary infarction site. Complex morphology occurs more

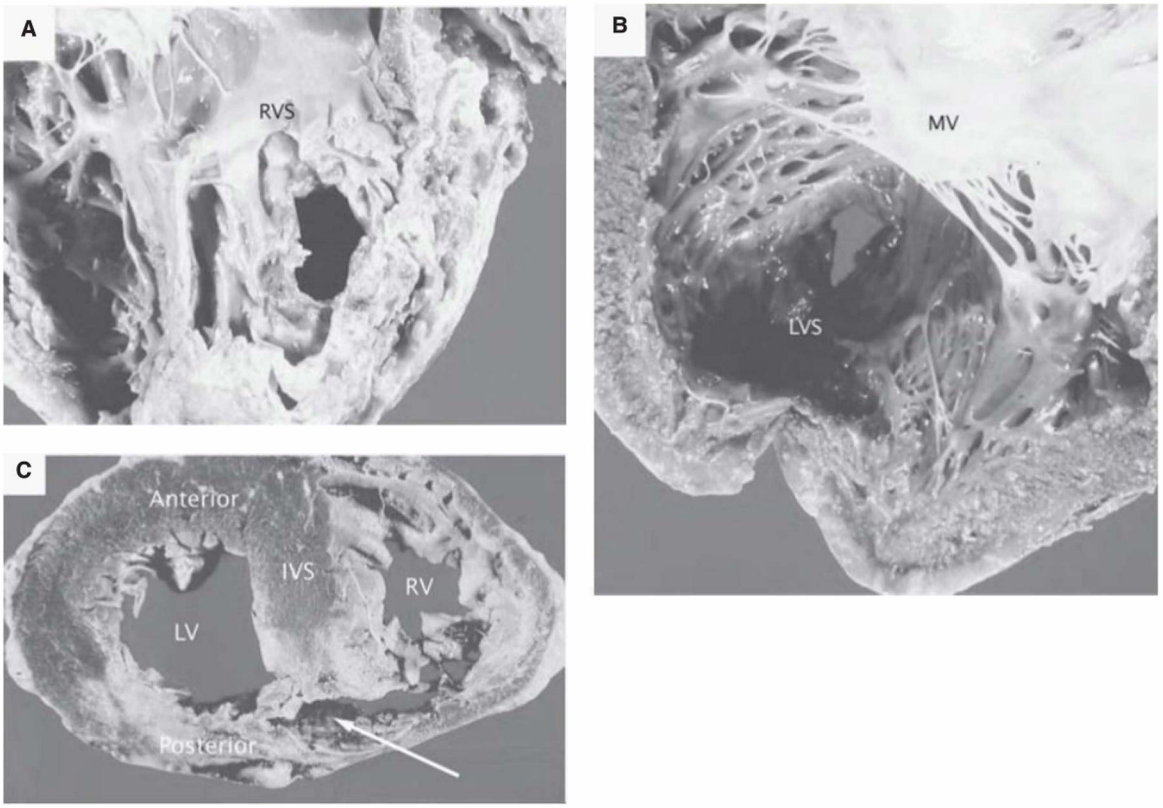



**FIGURE 31-17** Pathologic specimens of ventricular septal rupture. **A** and **B.** Simple ventricular septal rupture with a direct through-and-through connection across the septum. The perforation is at the same level on both sides of the septum. **C.** Complex septal rupture (*arrow*) after infarction of the basal inferior septum and adjacent ventricular wall. LVS, left ventricular aspect of the ventricular septum; RVS, right ventricular aspect of the interventricular septum; MV, mitral valve; IVS, interventricular septum; LV, left ventricle. (From Birnbaum Y, Fishbein MC, Blanche C, Siegel RJ. Ventricular septal rupture after acute myocardial infarction. *N Engl J Med* 2002;347(18):1426–1432.)

commonly with inferior infarcts, whereas anterior infarcts are associated with simple VSR.[333]

Anterior VSR usually occurs after acute occlusion of the LAD coronary artery and most often is located where the septum joins the free wall. Infarcted myocardium occupies a large section of the anterior portion of the septum. Inferior VSRs occur after occlusion of the right coronary artery. They may be located near the base of the heart, abutting the MV annulus, midway between the base and apex, or, less commonly, near the apex. Midseptal defects, usually resulting from occlusion of a large septal perforating artery, are rarer.

The size of the rupture varies considerably, from millimeters to centimeters, and in 5 to 11 percent of cases, multiple defects are present.[338] VSR may occur in combination with other mechanical defects, including PM or ventricular free wall rupture.[339] MR occurs in approximately 33 percent of cases but more often results from LV dysfunction than from PM rupture.[340]

## PATHOPHYSIOLOGY

Interventricular rupture results in a left-to-right shunt of variable magnitude and a significant biventricular hemodynamic load on an already ischemic heart. In most patients, this leads to progressive clinical deterioration, although small ruptures with small shunts may be better tolerated. Initially, the shunt manifests primarily as RV volume overload and increased pulmonary blood flow. Secondary LVvolume overload then results. The diversion of blood flow from the systemic to the pulmonary circulation ultimately leads to a low-output cardiac state; this may be more severe in patients with normally compliant right ventricles.[326] Systemic vasoconstriction in response to peripheral hypotension and hypoperfusion results in a worsening of the left-to-right shunt. A progressive spiral in cardiac function results, leading to worsening myocardial perfusion, increased myocardial workload, infarct extension, and ultimately end-organ hypoperfusion and cardiogenic shock. As the LV fails and systemic pressure declines,

the volume of the shunt ultimately decreases as cardiovascular collapse ensues.

## Clinical Features

Changes in the incidence of VSR after MI with the advent of reperfusion therapies have been associated with a change in the timing of presentation. Historically, most patients presented approximately 5 to 6 days after MI.[341] In the current era, the median time to rupture after MI is less than 24 h.[332] Risk factors for VSR after MI include advanced age, hypertension, and the absence of a history of MI or angina.[325,330,332,334–337,342,343] The influence of gender on the incidence of VSR is not clear. Many surgical series contain a preponderance of men,[344,345] and larger series have documented a higher incidence of rupture among women.[327,332]

The symptoms associated with VSR are those of myocardial ischemia, low cardiac output, and shock, particularly when these symptoms occur after resolution of the initial symptoms. Recurrence of chest pain and shortness of breath are common.[336] A harsh pansystolic murmur heard loudest at the left lower sternal border or a palpable parasternal thrill may be present in up to 50 percent of patients with acute VSR; however, the onset of cardiogenic shock may lead to a decrease in turbulent flow and a loss of the murmur.[328] ECG often demonstrates new ST-segment elevation.[336] The location of the infarct on ECG correlates well with the location of the septal rupture.[346]

## Diagnostic Modalities

In a patient with acute cardiovascular collapse after MI, the differential includes VSR, free wall rupture, and MR (with or without PM rupture) as well as acute ventricular dysfunction (Table 31-7).[339] Because free wall rupture has a very different presentation dominated by the signs of pericardial tamponade, the primary diagnostic dilemna with VSR is differentiating patients with MR from those with VSR; this can be made more difficult by the coexistence of these entities in up to 20 percent of patients.[347–349] Differentiation based on clinical examination is difficult, although clues to the existence of VSR include a palpable thrill that generally is not evident in MR and the lack of the severe pulmonary edema common to MR. However, in low-output states,

**TABLE 31-7: Clinical Characteristics of Ventricular Septal Rupture, Rupture of the Ventricular Free Wall and Papillary Muscle Rupture**

| Characteristic | Ventricular Septal Rupture | Rupture of Ventricular Free Wall | Papillary Muscle Rupture |
|---|---|---|---|
| Incidence | 1–3% without reperfusion therapy, 0.2–0.34% with thrombolytic therapy, 3.9% among patients with cardiogenic shock | 0.8–6.2%; thrombolytic therapy does not reduce risk; primary PTCA seems to reduce risk | About 1% |
| Time course | 3–7 days without reperfusion therapy; median, 24 h with thrombolysis | 1–7 days without reperfusion therapy; mean, 2.7 days with thrombolysis | Median, 1 day (range 1–14 days) |
| Clinical manifestations | Chest pain, shortness of breath | Anginal, pleuritic, or pericardial chest pain, syncope, hypotension, arrhythmias, nausea, restlessness, hypotension, sudden death | Abrupt onset of shortness of breath and pulmonary edema; hypotension |
| Physical findings | Harsh holosystolic murmur, thrill (+), $S_3$, accentuated second heart sound, pulmonary edema, RV and LV failure, cardiogenic shock | Jugulovenous distention (29% of patients), pulsus paradoxus (47%), electromechanical dissociation, cardiogenic schock | A soft murmur in some cases, no thrill, variable signs of RV overload, severe pulmonary edema, cardiogenic shock |
| Echocardiographic findings | Ventricular septal rupture, left-to-right shunt on color flow Doppler echocardiography through the ventricular septum, pattern of RV overload | >5 mm pericardial effusion not visualized in all cases, layered, high-acoustic echoes within the pericardium (blood clot), direct visualization of tear, signs of tamponade | Hypercontractile LV, torn papillary muscle or chordae tendineae, flail leaflet, severe mitral regurgitation on color flow Doppler echocardiography |
| Right heart catherization | Increase in oxygen saturation from RA to RV, large V waves | Ventriculography insensitive, classic signs of tamponade not always present (equalization of diastolic pressures among the chambers) | No increase in oxygen saturation from RA to RV, large V waves, very high pulmonary capillary wedge pressures |

PTCA, percutaneous transluminal coronary angioplasty; RA, right atrium; RV, right ventricle; LV, left ventricle.

From Birnbaum Y, et al. Ventricular septal rupture after acute myocardial infarction. *N Engl J Med* 2002;347(18):1426–1432.

these clues may not allow differentiation between the two complications.

Historically, right heart catheterization was the diagnostic tool of choice for distinguishing these entities.[350] In VSR, RV oxygen saturation is increased, whereas the increase in MR is confined to the pulmonary artery vasculature. However, advances in both transthoracic and TEE have led to their supplanting right heart catherization in the diagnosis of VSR. Doppler echocardiography can identify the site and size of left-to-right shunts through the septal defect accurately, and sensitivity and specificity as high as 100 percent have been reported in the differentiation of VSR from MR (Fig. 31-18).[351,352] In addition, echocardiography can be used to assess the degree of both right and left ventricular impairment in these patients.

LV catheterization with angiography has both advantages and disadvantages. Angiography is time-consuming, and the load of contrast dye may be detrimental to both renal and ventricular function; in patients with significant end-organ hypoperfusion, this is an important concern. However, when concomitant coronary revascularization is being considered, angiography helps delineate coronary anatomy. As many as 60 percent of patients with VSR may have significant disease in coronary arteries other than the one perfusing the affected portion of the septum, and revascularization may improve long-term survival.[353] Therefore, if the patient's condition permits, preoperative coronary angiography should be performed.

## Medical Therapy

Medical therapy consists of both mechanical and pharmacologic support of cardiac function and end-organ perfusion. In most cases, after the diagnosis of VSR, these therapies are merely temporizing measures. They may allow for the performance of further diagnostic procedures (including cardiac catheterization when appropriate) and maintenance of perfusion en route to the operating room, but operation remains the only definitive treatment.

The goals of medical therapy in this setting are (1) maintenance of end-organ perfusion, (2) optimization of coronary perfusion, (3) reduction in myocardial oxygen demand, and (4) reduction in SVR to minimize the left-to-right shunt. In patients without hypotension, vasodilators such as nitroprusside may be useful in reducing SVR; however, they may cause a significant decrease in coronary perfusion as well as end-organ compromise if hypotension occurs.[53] Diuretics may help reduce SVR and preload without similar effects on coronary perfusion. Although inotropic agents may be required to maintain systemic blood flow (and nearly all patients with cardiogenic shock and VSR require them),[332] the increase in systemic pressure may worsen shunting and exacerbate the shift in blood flow from the systemic to the pulmonary circulation. IABP remains the only method that can accomplish all these goals. Counterpulsation decreases LV afterload, which reduces the right-to-left shunt while augmenting cardiac output and end-organ perfusion. Through diastolic augmentation, coronary perfusion is maximized. The advantages of IABP suggest that an IABP should be inserted into all patients with VSR and hemodynamic compromise. Although it cannot treat VSR in the long term, it may provide enough time to perform cardiac catheterization, and it optimizes the patient's hemodynamic status before the induction of anesthesia. IABP improves hemodynamics in all patients with VSR, and those patients tolerate counterpulsation well without loss of the beneficial effect with insertion times longer than 24 h.[354]

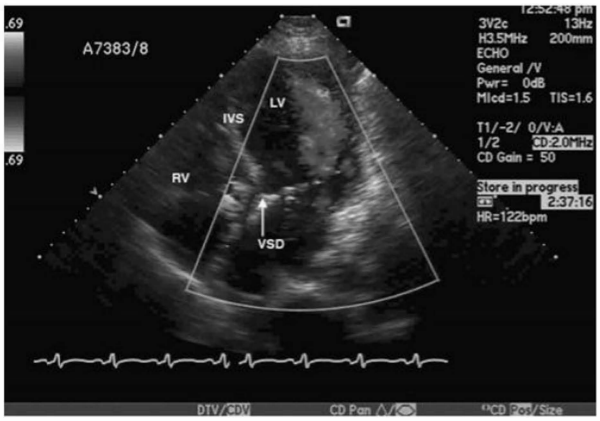



**FIGURE 31-18** Doppler echocardiography demonstrating an ischemic ventricular septal rupture with flow through the ventricular septum during systole. LV, left ventricle; RV, right ventricle; IVS, interventricular septum; VSD, ventricular septal defect.

## Surgical Therapy

### TIMING OF SURGERY

The first successful repairs of VSR were performed in patients more than 1 month after the rupture event.[324–356] It was felt at that time that patients would not tolerate earlier repair both because of their poor hemodynamic status and because it was felt that recently necrosed myocardium would not hold sutures. Those successes, as well as the abrupt acute decompensation and clinical deterioration in other patients, led to the belief that patients with VSR should not be operated on for 1 month after rupture. However, delayed surgery after rupture probably simply selected out patients with smaller defects and relatively preserved hemodynamics whereas patients with more severe disease died during the delay.[357,358] Patients who were not operated on were unlikely to survive the hospital stay, and many patients underwent operative repair only after cardiovascular collapse; 4-week mortality without operation is 80 to 90 percent, and 1-year mortality approaches 100 percent.[327,358,359] More recent data from the SHOCK registry confirm the poor outcomes in critically ill patients with VSR who do not reach operative

repair. The registry followed 55 patients with cardiogenic shock secondary to VSR; 24 were managed medically, and 31 underwent high-risk surgery. Overall survival was 28.6 percent among those treated surgically but only 4.2 percent among those treated medically.[332] Because of these dismal outcomes, attempts were made to operate earlier, and in 1977, Daggett and associates reported increased survival in 43 patients operated on early for VSR.[357] Early operation also may decrease the risk of subsequent free wall rupture, which often is preceded by VSR.[336] Since that time, other authors have confirmed the relative survival advantage of early operation in these patients, and operation within 24 to 48 h has become the standard.[360]

Patients presenting after VSR can be grouped broadly into four groups on the basis of hemodynamic status at the time of diagnosis. The first group consists of the few patients who remain hemodynamically stable and in whom a small left-to-right shunt is well tolerated without hemodynamic support or end-organ compromise. These patients may be managed medically until it is convenient to perform the repair, but operative repair should be performed before hospital discharge. The second group consists of patients in cardiogenic shock. This is the largest group of patients with VSR.[327,361] Another large group of patients occupies an intermediate position between those in the first two groups; these patients require operation within 12 to 24 h. Their clinical stability on initial presentation should not lead to medical management or an attempt to delay operation; further deterioration will result, and the patient will require emergent and risky surgical repair. The final group consists of patients who present after the onset of end-organ damage or sepsis. These patients are not likely to survive surgery, and there are case reports of survival using long-term IABP support until they can tolerate operative repair.[362]

## OPERATIVE TECHNIQUE

***General Considerations.*** After median sternotomy, CPB is initiated swiftly with bicaval cannulation. LV venting is not required, as the LV should vent spontaneously via the septal defect and insertion of a vent may dislodge any mural thrombus present in the LV. For the same reason, manipulation of the heart before clamping should be minimized. As with other patients undergoing cardiac operations in proximity to myocardial ischemia, both retrograde and antegrade cardioplegia should be used. Distal coronary anastomoses should be performed before ventriculotomy; this both maximizes myocardial protection and minimizes manipulation of the fragile ventriculotomy repair.

The surgeon often is challenged by the weak and friable myocardium in both the septum and the infarcted regions of the ventricular free wall. These regions have a tendency to weaken, fail, and lead to a residual defect. The use of a generous pericardial patch is important in reducing tension and decreasing the risk of a residual or recurrent septal defect. The closure of the left ventriculotomy, particularly when large free wall infarcts are present, must be performed with large 1-cm bites of tissue and extensive use of felt buttressing to decrease the risk of postoperative free wall rupture.

***Surgical Approach to Interventricular Septal Rupture.*** The first repair by Cooley and associates[324] involved a right ventriculotomy for access to the interventricular septum, as was used in the approach to congenital VSR. Unfortunately, this approach has multiple disadvantages: (1) Exposure of the defect is not optimal, (2) damage occurs to the normal myocardium of the right ventricle, (3) collateral blood flow from the right coronary circulation is cut off, and (4) it fails to address the portion of infarcted LV wall that results in paradoxic bulging during ventricular systole. With these weaknesses in mind, Heimbecker and coworkers[363] developed the technique of left ventriculotomy; this allows simultaneous repair of the septal defect along with infarctectomy and aneurysmectomy. This has become the standard surgical approach to most VSR repairs.

***Apical Septal Rupture.*** The technique of apical rupture repair is perhaps the most simple, but apical VSRs are rare. Daggett and coworkers first described the technique of apical amputation in 1970.[364] An incision is made through the necrotic LV apex and through the septum and the RV free wall. This results in amputation of the apex of the heart. The repair is completed by approximating the ventricular free walls to the septum, using Teflon felt strips and horizontal mattress sutures (Fig. 31-19).

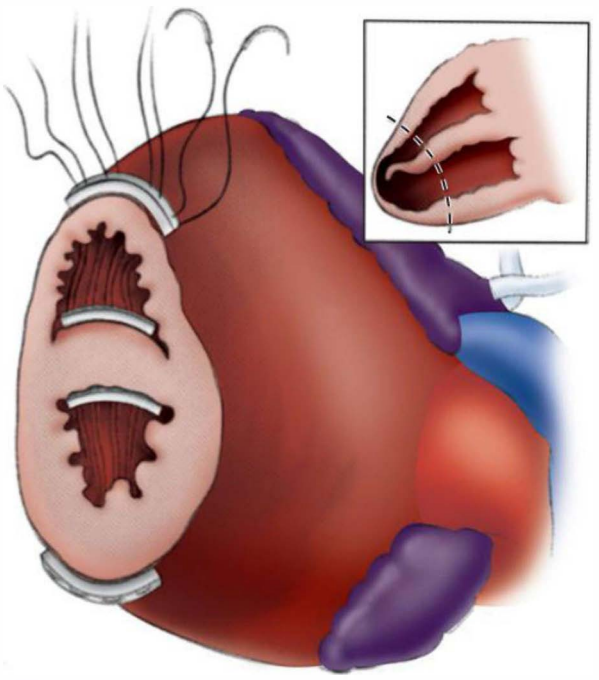


**FIGURE 31-19** Amputation of an apical septal rupture with biventricular closure using pledgeted sutures. (Adapted from Fig. 22.11 in Buxton BF, Frazier OH, Westaby S (eds). *Ischemic Heart Disease Surgical Management*. Philadelphia: Mosby, 1999.)

***Anterior Septal Rupture.*** The initial approach to anterior septal rupture is via a transinfarct left ventriculotomy with infarct excision. Some small anterior defects may be closed without a prosthetic patch by approximating the free anterior edge of the septum to the RV free wall with mattress sutures of Tevdek over strips of felt. However, most defects require the insertion of a patch to obtain a tension-free repair.

The classical technique involves debridement of the VSR and if necessary slight enlargement of the defect. This permits the placement of horizontal mattress sutures from the RV side of the defect through a thick felt patch and then through the septum. The sutures then are passed through the patch approximately 8 mm from the edge and tied into place. The patch is brought out through the ventriculotomy incision, and the incision is closed. Wide bites of viable LV wall are taken, and the closure is buttressed with large felt patches. In this technique, if there is not sufficient anterior septum to anchor the anterior portion of the patch, horizontal mattress sutures may be passed from the epicardial to the endocardial surface of the right ventricle to complete the repair.

As surgical repair has occurred earlier, the strength of the myocardium holding the patch sutures has become a significant issue. Although sutures should be placed into viable myocardium, in the first 24 h after infarct it may be difficult to differentiate viable from nonviable regions. The addition of tissue adhesives to repair techniques adds strength and theoretically reduces the risk of postoperative dehiscence of the septal patch. Seguin and associates described the first use of fibrin sealant in reinforcing patch closure of VSR in three patients.[365] Refinements in technique and biological adhesive have led some authors to advocate the repair of VSR with a pericardial patch and gelatin–resorcinol–formaldehyde (GRF) biological glue.[366] In this technique, placement of the patch is similar to that in the classic approach. However, the sutures anchoring the patch to the septum are placed at a wider radius to ensure attachment to viable myocardium. This suture is a running suture without pledgets. GRF glue is applied over the septal side of the pericardial patch through to the ventriculotomy closure. Excellent results have been obtained with this technique, and successful repair of cardiac rupture without the use of sutures has been reported.[367–370] There has been theoretical concern that the formaldehyde might inhibit ventricular remodeling and growth of fibrous tissue into the patch area. Although autopsy studies have not demonstrated that problem,[368] the next generation of glues promises to alleviate this theoretical concern.

***Posterior Septal Rupture.*** The repair of inferoposterior septal defects is made more difficult by exposure of the posterior of the heart as well as the proximity of both the PDA and, on the endocardial surface, the posteromedial PM. After cross-clamping, the heart is retracted out of the cardiac well and the posterior surface is exposed. A left ventriculotomy is made through the infarct approximately 1 cm lateral to the PDA, with care taken to leave the PMs undamaged. The patch then is cut and secured with running 4-0 monofilament sutures. As with anterior defects, the patch then may be brought out through the ventriculotomy and secured.

Inferior infarctions with significant LV free wall enlargement require additional techniques. In these cases the infarcted ventricular wall often is thinned out. Use of this weakened myocardium for closure increases the risk of rupture. To strengthen the repair, the ventriculotomy is closed with a Dacron free wall patch backed with pericardium. The patch is secured to the ventricular wall with interposed felt strips on both the epicardial and the endocardial surfaces to strengthen the attachment points.

***Repair by Infarct Exclusion.*** Athough emergent operative treatment for VSR provided an improvement over the nonoperative management of these patients, mortality rates remained high, exceeding 30 percent in nearly all large series.[326,358,371] The recognition of the importance of LV geometry to appropriate LV function led to a desire to avoid resection of infarcted myocardium as much as possible. This is especially important because patients with higher shunt flow, and therefore better ventricular function, have improved survival rates after VSR repair.[371] David and colleagues[372] and others[373–376] developed the technique of infarct exclusion to exclude the defect and infarcted myocardium from the high-pressure LV system without resection of regions of myocardium, thus preserving normal LV function as much as possible.

As with the techniques discussed above, bicaval cannulation is performed and antegrade and retrograde cardioplegia is given. Occluded coronaries are bypassed before the ventriculotomy is begun. For anterior septal defects, an incision is made in the apex of the LV and extended toward the base of the heart approximately 1 cm lateral to the LAD coronary artery through the ventriculotomy. Stay sutures are placed into the ventricular wall to provide exposure, and the endocardial surface is examined. A glutaraldehyde-fixed pericardial patch is cut to fit over the entire extent of infarcted myocardium (in most patients this is approximately $4 \times 6$ cm[372]). Starting at the lowest and most proximal part of the septum, the patch is secured to healthy myocardium with 3-0 polypropylene sutures in a running fashion (Fig. 31-20). Another suture starting at the same point secures the opposite side of the patch to the noninfarcted portions of the anterolateral LV wall. When the two suture lines meet, the sutures are tied to each other, and the infarcted myocardium becomes excluded from the left ventricle. Closure of the ventriculotomy then proceeds with a buttressed repair of horizontal mattress stitches.

If the infarction extends into the base of the anterior PM, it may not be possible to exclude the infarct completely from the LV cavity. In this case, the suture line is brought through the myocardium and buttressed on the epicardial surface with Teflon or pericardial strips. Other authors recommend passing all sutures through to the epicardial surface; in the region of the defect, the suture is passed through the septum and then through the RV free wall to allow buttressing at the epicardial surface.[373]

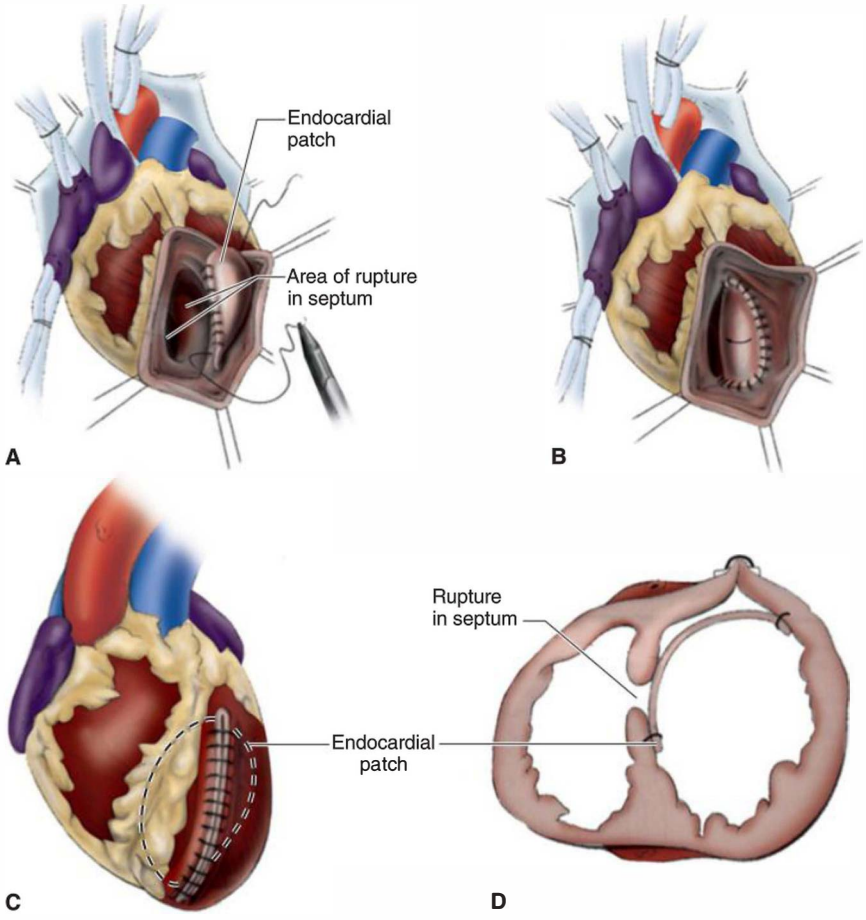



**FIGURE 31-20** Repair of an anterior septal rupture with an endocardial patch and infarct exclusion. An oval pericardial patch is sutured to the septum and lateral wall to exclude the infarcted muscle from the left ventricular cavity. (Modified from David TE, Dale L, Sun Z. Postinfarction ventricular septal rupture: repair by endocardial patch with infarct exclusion. *J Thorac Cardiovasc Surg* 1995;110(5):1315–1322.)

Repair of a posterior VSR is performed with a similar goal—exclusion of the infarct region from the LV cavity—although as with patch repairs, the proximity of the PMs increases the difficulty of these repairs. The initial incision is made through the posterior wall of the left ventricle, 1 to 2 cm lateral to the PDA, and extended to within 1 cm of the mitral annulus. The incision also is extended toward the apex and the base of the posterior PM. Stay sutures are secured to the ventricular wall; in particular, a suture securing the apex of the heart in the direction of the upper part of the sternotomy facilitates adequate exposure.[377]

The posterior patch is cut in the shape of a triangle to encompass all of the infarct (usually approximately 4 × 7 cm). The base of this triangular patch is secured to the fibrous annulus of the MV, beginning at the middle of the posterior leaflet and extending toward the medial commissure until healthy septal myocardium is reached. The patch is trimmed as needed and sutured to healthy endocardium, using a continuous 3-0 polypropylene suture extending toward the apex of the heart. Finally, the medial side of the patch is sutured to the posterior wall of the left ventricle, using interrupted full-thickness bites buttressed on the epicardial side with a Teflon strip. This excludes the infarct zone from the LV cavity, and the ventriculotomy is closed with buttressed interrupted sutures.

A recent modification of infarct-exclusion included the use of a double-patch technique in which the VSR is closed with a small pericardial patch before insertion of the infarct-excluding patch.[367,378] The inter-"patch" space then is filled with glue. The theoretical advantages of this technique include a more physiologic reconstruction of the interventricular septum, avoidance of contact between tissue adhesive and the systemic circulation, and decreased tension on the infarct-excluding suture lines.[367] Whether these benefits are worth the extra time required for placement remains to be established.

### CONCOMITANT CORONARY ARTERY BYPASS

Reports of coronary artery bypass during repair of VSR describe conflicting results. The disadvantages of concomitant CABG include risk of preoperative left heart catheterization in hemodynamically compromised patients and the prolonged operative and CPB times. Although some authors have reported decompensation among approximately 5 percent of patients undergoing angiography,[379] more recent reports suggest that preoperative angiography is not associated with adverse changes in hemodynamics or clinical status.[361,380] Other authors question the value of angiography in the setting of VSR. Although in many series most patients have single-vessel disease,[379,381,382] this is not universally true,[361] and even when it is, as many as 45 percent of patients have multivessel disease. Even patients with anterior infarction and without a previous history of ischemic heart disease do not *invariably* have single-vessel disease.[361] Thus, routine angiography in this population appears to carry little additional risk and may provide useful information; in addition, it allows guided placement of an IABP for hemodynamic stabilization.

Independent of the risk of angiography, some authors question the utility of coronary revascularization in this population. The data in this respect are not clear; however, although many studies have not shown a survival advantage among patients undergoing concomitant CABG, they also have not shown a detrimental effect of CABG despite longer operative and bypass times.[381,383] Other studies have shown improvements in middle- and long-term survival with concomitant CABG.[361,384] Data do not demonstrate a definitive survival advantage, but no disadvantage to preoperative angiography and concomitant CABG has been demonstrated. The authors recommend routine angiography and bypass of severe proximal stenoses in these patients.

### PERCUTANEOUS CLOSURE OF SEPTAL RUPTURE

Because of the poor clinical status of patients with VSR, percutaneous closure of the defect offers notable advantages in that it does not require operation and CPB and does not have the potential for dehiscence of the ventriculotomy closure that results in rupture. Several case reports have described the successful use of the Amplatzer ventricular septal closure device in residual defects after surgical repair.[385–390] In addition, a recent case report demonstrated successful intraoperative deployment of the device under direct vision through a right atriotomy providing primary repair of VSR.[391] The use of percutaneous devices in the acute postinfarct period has been less successful, and all survivors who had not had previous surgeries had transcatheter closure remote from their infarcts.[390,3392] It is likely that the soft, friable edges of the defect do not provide an adequate anchor for the device, leading to residual shunting and hemodynamic deterioration.[393] Further refinements in techniques are necessary before percutaneous closure of VSR becomes routine, although its use in closure of residual postsurgical defects appears warranted.

### VENTRICULAR ASSIST DEVICES

The use of VADs for hemodynamic support in these patients as a bridge to transplantation is challenging. It may be difficult to secure the cannulas to the postischemic necrotic heart. There are case reports of VAD placement as early as 7 days after MI for postrepair residual defects.[394] However, the use of VADs in the provision of hemodynamic support for patients with an unrepaired VSR has been less successful. One concern particular to patients with VSR is an increase in right-to-left shunting that results in hypoxia and cerebral hypoperfusion.[395] VADs also may be helpful as a bridge to recovery in patients who cannot be weaned from CPB. Biventricular support may be required both in patients with RV infarction and in those with residual defect (to prevent an increase in right-to-left shunting), and also may be used as a bridge to surgical repair.[396]

## Outcomes and Prognosis

### POSTOPERATIVE MORTALITY

Several large series have examined outcomes in surgery for VSR. In-hospital and 30-day mortality rates are between 20 and 50 percent even in recent series.[326,345,358,361,371,372,380,381,383,397–401] Preoperative characteristics significantly affect the risk of negative outcomes after surgery. The most important predictor of postoperative survival remains preoperative hemodynamic status.[361,372,380,381,400,401] Although measured in a variety of ways (including the presence of cardiogenic shock,[372,381,400,401] the need for inotropic support,[361,380] and the presence of renal failure[372]), increased mortality invariably is seen in patients with poor preoperative cardiac function. Other variables that affect early postoperative survival include posterior infarct location,[398,400] total occlusion of the infarct-related artery,[361] and RV infarction[380] or failure.[372] The poor prognosis of patients with posterior infarcts and VSRs has been attributed to the coexistence of MR in those patients, the increased technical difficulty of repair, and the associated RV infarction.[357,383,402,403] Older age, particularly in patients with poor preoperative clinical status, predicts poor outcomes in some studies,[338,357] but this has been a variable finding.

### IMPACT OF OPERATIVE TECHNIQUE

Mortality rates vary widely among reported series. Other groups have had difficulty replicating the outcomes of the Toronto group with infarct-exclusion. In their experience, no deaths occurred in patients without cardiogenic shock, and overall mortality was only 14 percent.[372] Unfortunately, others have had mortality rates ranging from 30 to 60 percent with similar repairs.[338,404] Similarly, the publication by Skillington before the development of infarct-exclusion reported an

overall early mortality rate of only 20.8 percent (mortality in the 2 years immediately before the report had declined to 11.1 percent)[405]; other groups using similar techniques have been unable to duplicate those excellent results.

In light of the small samples in even the largest retrospective studies, changes in practice over time that make any single series unlikely to contain a single operative repair, a wide variety in referral patterns, differences in criteria for operative candidates, and the timing of operation, comparison between series is of little value. These rather than other factors probably explain differences in outcomes even when similar repairs are used.

### CAUSES OF EARLY MORTALITY

In most series, approximately 5 to 10 percent of patients cannot be weaned from cardiopulmonary support in the operating room.[372,381,398,401] Progressive cardiac failure with a low-output state is the most common cause of postoperative death (50 percent of early mortality), and some degree of failure is present in nearly all patients during the postoperative period.[345,380,381,398] Other causes of death include postoperative free wall rupture, recurrent VSR, severe MR, bleeding, sepsis, cardiac arrest, respiratory failure, and multiple organ system failure (each accounts for 5–10 percent of mortality, depending on the series).[380,381,398,401,406] The type of repair performed does not appear to affect the relative frequencies of these causes of postoperative mortality.

### OTHER COMPLICATIONS

In most series, recurrence of the VSR occurs in approximately 20 to 30 percent of patients,[345,361,381,401] although the Toronto series of infarct-exclusion contains only a single recurrence with a small residual shunt in 44 cases.[372] The range of recurrence depends on the modality used to detect it. Close echocardiographic follow-up may detect recurrence in nearly 50 percent of patients, but most of these events are not clinically significant and may not influence survival.[381] Patients with small residual defects who are hemodynamically stable may be managed conservatively. In the large series reported by Deja and associates, 14 patients out of the 44 with echocardiographically detected shunts required reoperation.[381] Mortality in patients with clinically significant recurrence approaches 10 percent.[381,405] The double-patch technique has been reported to decrease the recurrence rate in some series,[380] but as with mortality, comparisons between series have little value and further experience with this technique is required. As was noted above, some patients may benefit from percutaneous closure of recurrent or residual defects.[385–390] MR occurs in approximately 2 percent of patients.[381] Other complications are those common to all emergent cardiac surgery, including sternal dehiscence (2 percent), reoperation for bleeding (6 percent), renal failure requiring hemodialysis (25 percent), arrhythmias requiring temporary (27 percent) or permanent pacemakers (1 percent), and stroke (5 percent).[381]

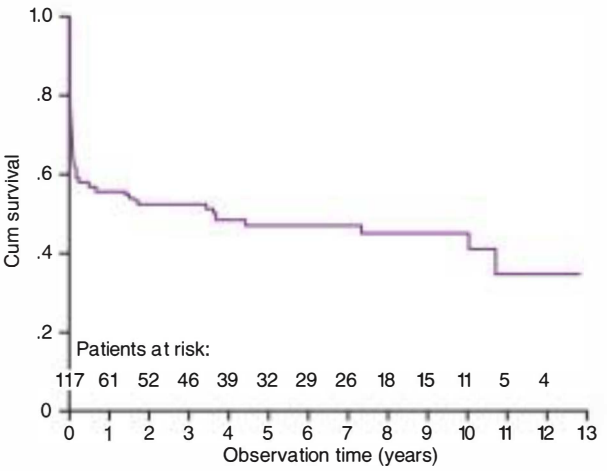



**FIGURE 31-21** Kaplan-Meier survival curve illustrating long-term survival after surgical treatment of ventricular septal rupture. (From Deja MA, Szostek J, Widenka K, et al. Postinfarction ventricular septal defect—can we do better? *Eur J Cardiothorac Surg* 2000;18(2):194–201.)

### LATE RESULTS

Although operative mortality and 30-day mortality are high, hospital survivors have excellent long-term outcomes, especially when their baseline medical status is accounted for (Fig. 31-21[381]). The overall 5-year survival is approximately 50 to 60 percent in recent series.[361,380,381] However, among hospital survivors, 2-, 5-, and 8-year survival of 85, 63, and 61 percent has been reported.[380] Functional status is also impressive: The majority of long-term survivors (70–95 percent) are in NYHA class I or II.[372,380] Late results of earlier repairs are equally striking: Davies and coworkers reported 37 percent survival at 14 years with 82 percent of the survivors in NYHA class I or II.[407]

## Summary

VSR occurs in the week after a large MI that results in a necrotic and weakened portion of the ventricular septum. The patients at highest risk are those who angiographically have single-vessel coronary disease without significant collateralization. Clinically, patients present with recurrence of chest pain, and a new harsh pansystolic murmur may be audible. Medical therapy should be used to stabilize the patient and allow for the performance of a diagnostic workup that includes an echocardiogram. Placement of an IABP improves outcomes through reduction in afterload and improvement in shunt dynamics. Although some patients with small, well-tolerated shunts may be managed conservatively, most patients should undergo urgent operative repair. Multiple repairs have been advocated; postoperative mortality ranges from 20 to 50 percent, and comparisons between repairs have not been useful.

# VENTRICULAR FREE WALL RUPTURE

## Introduction

William Harvey first described ventricular free wall rupture (VFWR) in 1647. Subsequent authors, including Morgagni,[408] Malmsten and Duben,[409] Winsor,[410] Steven,[411] and Krumbhaar and Crowell,[412] further refined the understanding of cardiac rupture, including its relation to coronary occlusive disease, weakening of the myocardium, and recent MI. Despite this early description, the first successful operation was not performed until 1970. In that year, Hatcher and colleagues[413] reported successful repair of a right VFWR; this was followed shortly by successful LV repairs reported by FitzGibbon and associates[414] and Montegut.[415] However, despite improvements in cardiac care, survival after VFWR remains dismal. Although an uncommon complication of MI, it is the second leading cause of in-hospital death after cardiogenic shock.[416,417]

## Pathophysiology

Left VFWR commonly occurs on the anterior or lateral wall of the ventricle at the midpapillary level.[418,419] The endocardial tear is within 1 cm of the base of one of the PMs in 80 percent of cases.[418] Increased mechanical stress in this location probably results from the countering forces of systolic contraction and PM stretch. Rupture usually occurs at the boundary between viable and necrotic myocardium.[419] Most of these patients have multivessel coronary artery disease with complete occlusion or inadequate revascularization of a major coronary vessel.[420] Collateral circulation is usually absent.

Pathologically, Perdigao and associates[421] described four types of rupture:

- Type I: almost direct trajectory without extensive dissection or bloody infiltration of the myocardium
- Type II: multicanalicular trajectory and widespread myocardial dissection and bloody infiltration
- Type III: orifice of rupture protected by intraventricular thrombus or pericardial adhesions
- Type IV: incomplete epicardial, endocardial, or intramyocardial rupture in which the trajectory does not penetrate all layers.

However, the division by Becker and van Mantgem[422] of rupture into three types may be more useful clinically:

- Type I: an abrupt slitlike tear
- Type II: erosion of the infarcted myocardium at the border with viable muscle tissue
- Type III: early aneurysm formation.

These types correspond with the clinical division of ventricular rupture into acute, subacute, or chronic with pseudoaneurysm formation. Acute rupture occurs with sudden massive hemorrhage into the pericardial space and leads to circulatory collapse and death, often within minutes. Subacute rupture, a term first used by O'Rourke,[423] occurs after a smaller tear in the myocardium that may be sealed temporarily with thrombus or adhesions (Perdigao type III). Finally, chronic rupture occurs when blood leaks slowly from the ventricle. In this case, pericardial adhesions form and contain the rupture, resulting in a false aneurysm. The different time courses of these entitities may be affected by infarction location, as fatal cardiac ruptures tend to occur in the anterior and lateral walls, whereas pseudoaneurysm formation is more likely in the inferoposterior walls.[424] The pathogenesis of VFWR is not completely understood. However, increasing knowledge about myocardial repair after infarction provides some insights. After infarction, remodeling begins initially with leukocyte infiltration and clearance of necrotic debris; this leads to a process termed infarct expansion. Clearance of necrotic debris leads to regional thinning and dilatation of the infarcted region of myocardium.[425] Thinning leads to a reduction in the number of myocytes crossing the infarct zone and a corresponding decrease in the tensile strength of the ventricular wall. Dilatation causes increased wall tension (Laplace effect). Thus, infarct expansion results in a period of myocardial weakness (usually 1–4 days post-MI) when the myocardium becomes particularly susceptible to rupture. The importance of remodeling to the pathogenesis of rupture is demonstrated by reduced rupture rates in animal models with inhibition of the plasminogen/matric metalloproteinase system that is responsible for ventricular remodeling.[426,427] This period of weakness may be required for eventual scar tissue formation, as these mice also have poor long-term angiogenesis and scar formation in the infarct region.[426,427]

## Clinical Features

### ACUTE AND SUBACUTE RUPTURE

The incidence of VFWR peaks during the first week after MI. Autopsy studies suggest that 80 percent of ruptures occur within 7 days of MI,[419] and most acute rupture events occur within 48 h of admission.[428] In large retrospective studies, acute VFWR resulted in death a median of approximately 3 days after the onset of symptoms of MI.[416] Risk factors for VFWR include older age (usually more than 60 years),[419,429] female sex,[342,419,429–432] a history of systemic hypertension[419] without LV hypertrophy[419] or sustained hypertension during admission,[342] the presence of a pericardial rub or pericardial effusion,[429,433] sustained chest pain,[342,431] and the absence of previous MI or angina.[419,431]

The overall incidence after MI varies in reported series, as many patients are unlikely to be identified in clinical series because of prehospital death. In autopsy series, as many as 30 percent of MIs may be accompanied by VFWR.[430] In contrast, much lower rates (1–4 percent) are reported among patients surviving to hospital admission for MI.[342,413,417,431,434–437] However, even in these series, it accounts for 6 to 17 percent of in-hospital mortality.[413,431]

**TABLE 31-8: Sensitivity, Specificity, and Positive Predictive Value of Different Variables Used Alone or in Combination for Diagnosing a Postinfarction Ventricular Free Wall Rupture**

| | Sensitivity (%) | Specificity (%) | Positive Predictive Value (%) |
|---|---|---|---|
| Infarct site | | | |
| Anterior | 25 | 70 | 3.9 |
| Inferior | 68 | 54 | 6.7 |
| Lateral | 7.1 | 90 | 3.3 |
| Prior myocardial infarction | 3.5 | 75 | 0.6 |
| Bundle branch block | 32 | 74 | 5.7 |
| Pulsus paradoxus | 46 | 99 | 72 |
| ST–T-wave deviations | 32 | 85 | 10 |
| Syncope | 64 | 91 | 26 |
| Hemodynamic signs of cardiac tamponade ($CT_H$)[a] | 85 | 99 | 0.9 |
| Pericardial effusion (PE) | 100 | 77 | 17 |
| Intrapericardial echoes (IE)[b] | 93 | 99 | 81 |
| Echocardiographic signs of cardiac tamponade ($CT_E$)[c] | 93 | 99 | 93 |
| Combinations of signs | | | |
| Hemopericardium (Hp)[d] | 21 | 99 | 85 |
| PE + type I IE | 7.1 | 99 | 28 |
| Syncope or shock + PE + type II IE + $CT_{E+H}$ | 53 | 100 | 100 |
| Syncope or shock + PE + type I IE + $CT_{E+H}$ | 32 | 100 | 100 |
| Syncope or shock + PE + Hp + $CT_{E+H}$ | 7.1 | 100 | 100 |

$CT_H$, hemodynamic evidence of cardiac tamponade; $CT_E$, echocardiographic evidence of cardiac tamponade; IE, intrapericardial echoes; Hp, hemopericardium; $CT_{E+H}$, echocardiographic and hemodynamic evidence of cardiac tamponade; PE, pericardial effusion.

[a]Hemodynamic signs of cardiac tamponade were the presence of an increase in right atrial pressure and characteristic profile of right atrial pressure waveform (depressed *x* descent and blunted *y* descent).

[b]Intrapericardial echoes could be of two types: type I, a wide, thick undulating band overlying the heart suspended in a moderate to large pericardial effusion, and type II, a massive, homogeneous, and immobile structure impinging on adjacent cardiac chambers.

[c]Echocardiographic evidence of cardiac tamponade was present when right atrial diastolic and/or right ventricular early diastolic collapse was associated with either or both of the following findings: Doppler ultrasound findings of exaggerated tricuspid and pulmonic flow velocities and reduction of peak mitral flow velocity with the onset of inspiration and the opposite changes after the onset of expiration or inferior vena caval plethora with blunted respiratory variation.

[d]Pericardial fluid with hematocrit <25.

Acute rupture is characterized by the sudden onset of chest pain with rapid cardiovascular collapse and pulseless electrical activity caused by pericardial tamponade. These are accompanied by severe jugular venous distention with cyanosis. Death nearly invariably occurs within minutes.[438]

The distinction between these patients and those with subacute rupture has not been defined clearly, but in general, patients with subacute rupture are those in whom pericardial effusion and hypotension of variable severity are not accompanied by pulseless electrical activity and cardiac arrest.[423,439] This subacute form of VFWR occurs in approximately 30 percent of in-patient ruptures,[431,440,441] and early recognition may allow operative repair and increase survival. In this group, the gradual onset of symptoms of pericardial tamponade may be appreciated before the onset of cardiovascular collapse; however, marked jugular venous distention and pulsus paradoxus have been found in only approximately 30 percent[442] and 50 percent[439,443] of patients, respectively. A variety of other signs and symptoms may be present in these patients: arrhythmias (including transient pulseless electrical activity, bradycardias, tachycardias and ventricular fibrillation, syncope, hypotension, shock, and chest pain, which may be transient, prolonged, or recurrent.[423,439,442–446] The sensitivity and specificity of these signs vary (Table 31-8[443]). Particularly in diabetic patients, VFWR may present with sudden collapse from pericardial tamponade even in the absence of antecedent chest pain.[447] Sudden onset of cardiogenic shock in the post-MI period should prompt rapid echocardiographic evaluation to differentiate infarct extension from the various mechanical causes: MR, VSR, and VFWR. Especially in cases of right heart failure or when there are signs and symptoms of pericardial tamponade, rapid diagnostic pericardiocentesis may be indicated.

## CHRONIC RUPTURE WITH PSEUDOANEURYSM

Chronic VFWR with false aneurysm formation is a rare entity that usually develops within 3 months of MI.[448] Traditionally, this was thought to carry a high rupture risk, and immediate operative therapy was recommended.[449–451] However, in a review of 52 patients, Yeo and associates found no deaths caused by cardiac rupture in the 6 patients with post-MI pseudoaneurysm who were managed medically.[424] In another series, 1-year mortality among nine patients who were managed medically was only 22 percent and no patients had rupture of the pseudoaneurysm.[452] Similar results were

obtained in a review by Natarajan and colleagues of the 66 cases reported in the literature.[453] Unfortunately, because of its rarity, the natural history of chronic VFWR with pseudoaneurysm formation has not been defined clearly; the increasing use of echocardiography after MI may allow for the earlier diagnosis of more patients with this disease and allow for better evaluation of the need for operative therapy.

### IMPACT OF REPERFUSION THERAPY

Reperfusion, whether spontaneous or induced, reduces infarct expansion and decreases infarct size.[272,281,454,455] This would be expected to reduce the incidence of VFWR; however, in the case of thrombolysis, there has been concern that the transformation of bland infarcts into hemorrhagic infarcts may increase the risk of rupture.[456–458] In a meta-analysis of four studies, Honan and associates demonstrated a reduction in the risk of rupture when thrombolysis occurred within 7 h but an increased risk after late thrombolysis (after 17 h).[459] Becker and colleagues studied 5,711 patients, and although patients who did have a rupture incurred it earlier (between 6 and 12 h), overall there was no difference in the incidence of rupture when thrombolysis occurred between 6 and 24 h.[417] Thus, early thrombolysis is thought to have a beneficial effect by limiting infarct size and related necrosis and minimizing regions of transmurality.

In contrast, outcomes after percutaneous revascularization have been uniformly positive.[417,460,461] Comparing 762 patients undergoing angioplasty with 613 receiving thrombolysis, Moreno and associates showed a significant reduction in the incidence of cardiac rupture (odds ratio 0.46, 95 percent CI 0.22–0.96).[462] Importantly, increasing time to reperfusion is an independent risk factor for cardiac rupture, reinforcing the importance of timely delivery to the catheterization laboratory.[438] The superiority of percutaneous interventions probably results from improved perfusion without the hemorrhagic or fibrinolytic side effects of thrombolysis.[463]

## Diagnostic Modalities

A high index of suspicion in cases of arrhythmias before cardiogenic shock or the sudden onset of shock or severe chest pain is essential to initiating the diagnostic workup of and initial therapy for VFWR.

### ELECTROCARDIOGRAPHY, CLINICAL EVALUATION, AND RIGHT HEART CATHETERIZATION

Oliva and associates evaluated 70 patients with cardiac rupture and found that patients with rupture were more likely to have persistent, progressive, or recurrent ST elevation (61 percent) than were those with MI without rupture (22 percent, $p \leq 0.002$).[464] Failure of the T wave to invert or reversal of an inverted T wave was also more common among the group with rupture (94 vs 34 percent, $p \leq 0.02$).[464] Unfortunately, because rupture is a rare event, the positive predictive value of these ECG signs was only 58 and 66 percent, respectively.[464] The best predictors of rupture were clinical symptoms such as pericarditis, repetitive emesis, and restlessness or agitation; when two or more symptoms were present, the positive predictive value for rupture was 95 percent.[464] Other criteria for predicting rupture have been proposed: tachycardia greater than 100 beats/min with ST-segment elevation equal to or greater than 0.1 mV in lead $V_5$ (for inferior MI) or lead II (for anterior MI),[465] generalized ST-segment elevation (odds ratio for rupture 9.2),[325] and ST elevation in aVL (odds ratio for rupture 5.4).[466] Unfortunately, because of the relative rarity of cardiac rupture, the positive predictive value of all these criteria tends to be minimal.

Classically, the pericardial tamponade of VFWR should lead to equalization of pressures across the cardiac chambers. Pulmonary artery catheter pressures usually demonstrate evidence of right heart failure: elevated right atrial pressures, the possibility of equalization of right atrial and PCWPs (although pericardial clot may prevent the expected equalization of pressures[467]), and alterations in the right atrial pressure waveform (deep *x* descent and blunted *y* descent).[463] Any of these changes should prompt rapid echocardiography to rule out pericardial tamponade and rupture.

### ECHOCARDIOGRAPHY

Echocardiography is the diagnostic study of choice in patients with suspected VFWR. It is noninvasive, safe, easy to perform even at the bedside, and widely available. However, it does have limitations. As many as one-third of patients without rupture will develop pericardial effusions after MI,[468] and so the positive predictive value of pericardial effusion alone is relatively low (27.5 percent).[439] However, the absence of pericardial effusion virtually excludes VFWR as a possibility (Fig. 31-22A).[439] The presence of intrapericardial echoes consistent with blod clots increases the sensitivity and specificity for VFWR, but the positive predictive value is still only 70 percent, as those findings also may occur after infarction fibrinous endocarditis.[439,469] Echocardiography is also useful in ruling out other mechanical causes of acute hemodynamic collapse after MI, including PM or VSR.

The addition of Doppler measurements and contrast agents has increased opportunities to identify the site of ventricular wall rupture (Fig. 31-22B). Doppler may demonstrate flow from the ventricle into the pericardial sac (although as tamponade progresses, this becomes less evident). Contrast agents (such as air bubbles) may be seen in the pericardial space.[470]

### ANGIOGRAPHY

In the case of subacute rupture, few data support the use of preoperative angiography. Few long-term survivors undergo concomitant coronary procedures,[471,472] and many angiograms demonstrate normal coronaries other than the

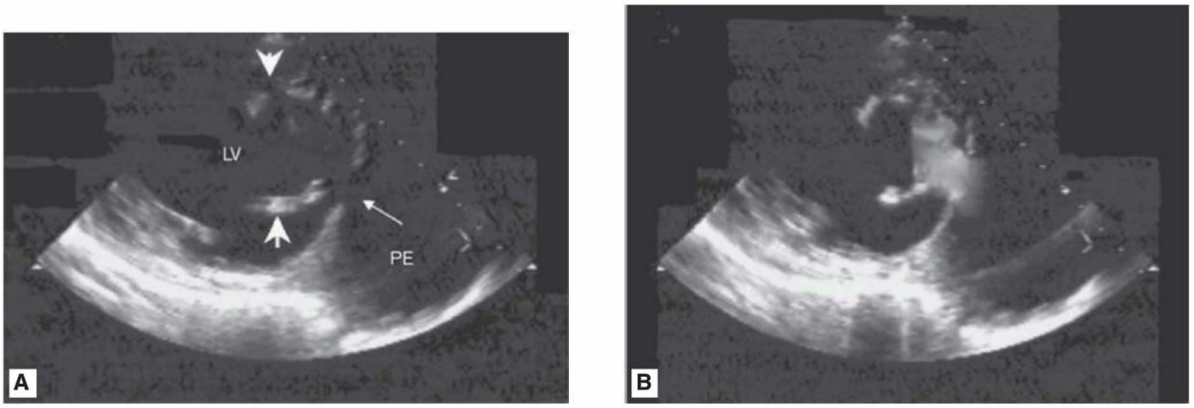



**FIGURE 31-22** Transesophageal two-dimensional (**A**) and Doppler (**B**) echocardiography illustrating ventricular free wall rupture (*white arrow*) into the pericardium from the left ventricle. White arrowheads mark the papillary muscles. Doppler imaging shows flow into the pericardium. PE, pericardial effusion; LV, left ventricle. (From Birnbaum Y, et al. Ventricular free wall rupture following acute myocardial infarction. *Coron Artery Dis* 2003;14(6):463–470.)

infarct-related artery.[473] Transfer to the operating room should not be delayed by cardiac catheterization, as outcomes depend on operative repair of the rupture rather than on concomitant coronary procedures.

### MAGNETIC RESONANCE IMAGING

Currently, magnetic resonance imaging (MRI) has little use in the setting of acute MI or subacute rupture because it is time-consuming and patients become relatively inaccessible inside the scanner. However, MRI is used with increasing frequency in the evaluation of pseudoaneurysms (Fig. 31-21). Its advantages include high resolution and image quality as well as excellent anatomic definition made possible by 3-D reconstruction techniques.[474–477]

## Medical Therapy

### ACUTE OR SUBACUTE RUPTURE

Once the diagnosis of VFWR has been made, medical management is directed toward hemodynamic stabilization. Initial therapies include aggressive IV fluid resuscitation and blood products as needed.[478] After initial stabilization, bed rest and β-blockade with maintenance of SBP between 100 and 120 may be helpful.[478] There are reports of long-term survivors without surgical repair, but those reports are rare.[478–480]

***Percutaneous Treatment.*** Pericardiocentesis is both diagnostic and therapeutic. It usually is performed with echocardiographic guidance. When pericardiocentesis demonstrates a serous pericardial effusion, rupture is excluded.[439] Therapeutically, pericardiocentesis decompresses the pericardium and decreases the threat of tamponade.[478] Despite this benefit, tamponade often recurs and proper drainage may be prevented by blood clots in the drainage catheter.[443,478] IABP placement may stabilize patients through improvements in both systemic and myocardial perfusion.[481] Murata and associates[482] described a novel technique for nonoperative management of VFWR. In two cases, injection of fibrin-glue into the pericardial space successfully stabilized patients, with resolution of pericardial effusion. Long-term follow-up of one patient treated with this technique revealed no restriction of LV motion.[483] Further experience with glue-based techniques will define the appropriate indications for such interventions, but it may be particularly applicable in patients with acute rupture, who previously would not have survived operative repair.[484]

### CHRONIC RUPTURE WITH PSEUDOANEURYSM

Traditionally, the risk of rupture led most patients with pseudoaneurysm to the operating room soon after diagnosis. However, increasing numbers of reports have described conservative management of some patients.[424,452,453] Unfortunately, no specific medical therapy has been recommended for those patients, although in light of a high incidence of stroke in the reported cases, some authors have recommended anticoagulation.[485]

## Surgical Therapy

### ACUTE OR SUBACUTE RUPTURE

In patients with acute or subacute rupture, immediate operative repair is indicated. Anesthetic induction in patients with cardiac tamponade may lead to sudden cardiovascular collapse as a result of peripheral vasodilatation. The patient should be prepared and draped before anesthetic induction. When necessary, mechanical cardiopulmonary support may be initiated via femoral cannulation before induction.[486,487] After induction, the chest and pericardium are opened rapidly, relieving the tamponade. The site of rupture is identified

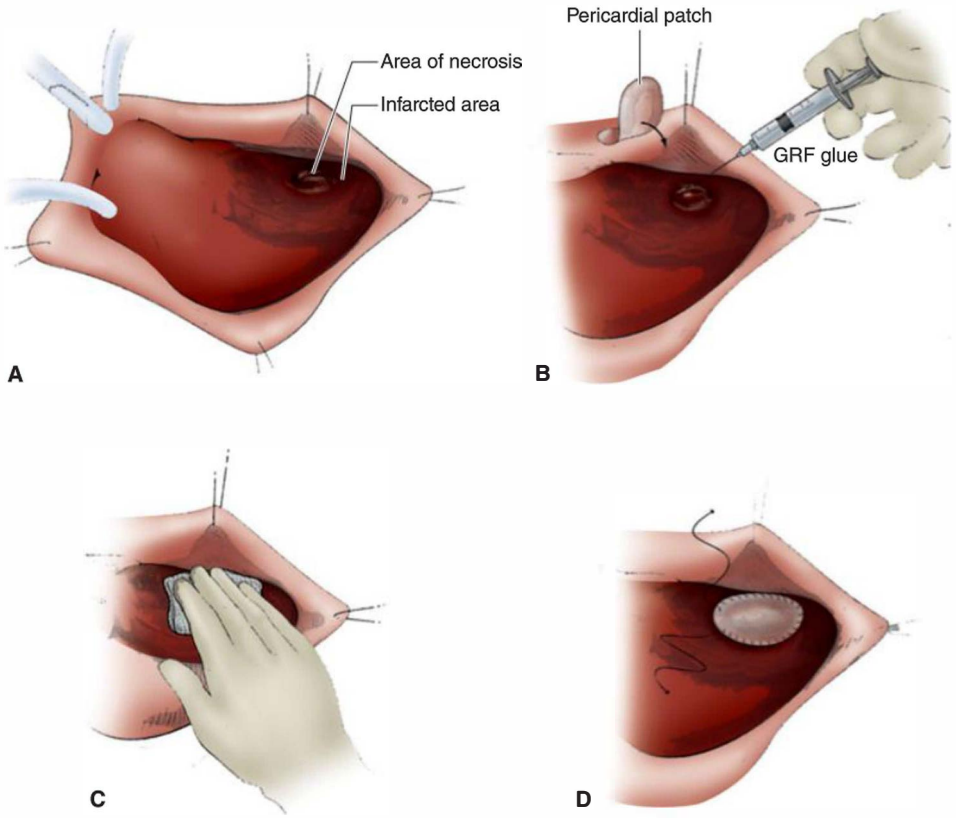



**FIGURE 31-23** Operative technique for onlay patch repair of ventricular free wall rupture. (Adapted from Figs. 21.1–21.4 in Buxton BF, Frazier OH, Westaby S (eds). *Ischemic Heart Disease Surgical Management*. Philadelphia: Mosby, 1999.)

rapidly, although in most cases the tear is sealed with clot and active bleeding will not be seen.

Several surgical approaches to the repair of left ventricular free wall rupture (LVFWR) have been advocated, including infarctectomy and patch closure, simple mattress suturing backed with felt, and an overlay patch sutured or glued into place with or without primary closure of the defect. Although many case reports describe acceptable outcomes with simple closure with pledgeted sutures,[446,488–490] in this repair the sutures are placed into necrotic myocardium; postoperative rupture would be a significant concern. Infarctectomy and patch closure do not have this shortcoming because the friable, infarcted myocardium is resected and sutures are placed into healthy tissue.[491–493] Early reports included simple closure of the defect after infarctectomy[414,473,481,494]; however, this may lead to a significant reduction in LV size and changes in LV geometry, in which case closure with a prosthetic patch is preferred. The disadvantages of this technique include the need for CPB and, at least theoretically, changes in LV geometry that may have negative long-term consequences in ventricular function, as has been seen in repair of VSR with infarctectomy.[372]

Nunez and associates were able to avoid the infarctectomy through primary closure of the defect with pledgeted sutures followed by placement of an onlay patch sutured to healthy myocardium (Fig. 31-23).[495] This technique provided good control of ventricular hemorrhage, and those authors reported survival out to 10 months.[495] Others have used similar onlay patches but have chosen not to close the myocardial tear; the patch can be secured with biological glue or sutures.[370,439,472,493,496–503]

With the advent of biological glue, many surgeons have begun to avoid the use of CPB in these patients. In posterior ruptures, CPB often is required, but with anterior ruptures, adequate closure can be obtained on the beating heart by using onlay patches secured with glue.[500] This technique appears to be safest when used in patients without a macroscopic defect in the myocardium.[504] In contrast, CPB is required when concomitant cardiac procedures are planned. Opinions about the need to perform CABG during repair of VFWR vary. Because 80 percent of ruptures occur in patients with multivessel coronary disease,[419] some authors advocate initiation of CPB and bypass of all major vessels before repair of the rupture.[488] However, as was noted above, preoperative angiography is not likely to be possible, and most reported long-term survivors have not undergone concomitant bypass procedures.[471–473] The experience with this disease is too limited to make definitive recommendations, and surgeons will

have to be guided by the clinical condition of the patient; some authors recommend a "middle ground" of bypassing palpable or clinically evident disease.[463]

### CHRONIC RUPTURE WITH PSEUDOANEURYSM

As was noted above, the natural history and risk of rupture with pseudoaneurysm are not clearly defined, and the timing of surgery depends on the perceived risk of rupture. In particular, chronic smaller pseudoaneurysms that are stable in terms of size may have a lower propensity for rupture, and patients may do well with conservative management.[424] However, surgical therapy remains the treatment of choice in patients likely to tolerate the operation. Since many patients with chronic pseudoaneurysms will be identified during a workup for coronary artery or MV disease, the decision to operate may be based on the coexistent disease.

Pseudoaneurysms may be repaired with either primary closure of the (usually thin) neck[475,505] or endocardial patch repair[475,506–508] similar to that used in a true LV aneurysm (see below). In the acute setting, the neck may not have sufficient fibrosis to provide an anchor for sutures, and so patch repair is probably a better option. When the myocardial defect is large, patch repair is preferred to minimize changes in LV geometry and relieve tension on the repair.

## Outcomes

### ACUTE AND SUBACUTE RUPTURE

The short- and middle-term results of onlay patch operations appear to be excellent. Lopez-Sendon and associates reported the results of 33 operations for ventricular rupture repaired with an onlay patch secured with either glue or sutures; 76 percent of the patients survived the operation, and long-term survival (mean follow-up 30 months) was 48.5 percent.[439] Canovas and associates recently reported middle-term outcomes for 17 patients with glued onlay patches: operative (30-day) mortality was 23.5 percent (4 of 17 patients), with one death resulting from patch failure.[500] Middle-term follow-up revealed only two additional deaths, and echocardiography revealed good ventricular function in the survivors.[500] Others have reported operative survival as high as 100 percent, although patient selection probably played a large role.[472]

### CHRONIC RUPTURE WITH PSEUDOANEURYSM

Because of its rarity, outcomes after surgical repair of ventricular pseudoaneurysm have been variable. The largest series, examining the 266 cases reported in the literature, found operative mortality of 23 percent; however, medical therapy had a 48 percent mortality rate.[485] Unfortunately, since this was a review of all *reported* cases, publication bias makes these numbers difficult to interpret. Outcomes from ventricular aneurysms may have to be relied on in estimating operative risk in this population.

## Summary

Ventricular free wall rupture is a devastating complication of MI; although it occurs uncommonly, it is the second leading cause of in-hospital death after MI. Clinical prediction of patients likely to have rupture is poor; echocardiograms should be obtained when there is any degree of suspicion. When rupture does occur, pericardiocentesis may be both diagnostic and therapeutic and may allow time for operative repair. Survival without operative repair in the setting of acute rupture is uncommon. Operative techniques include closure of the defect with or without an onlay patch. Many authors advocate sutureless repair with biological glue to adhere the patch to the epicardium. The results of onlay patch operations are excellent, with operative mortality of approximately 25 percent and little longer term mortality. Rarely, patients also may present with chronic rupture and pseudoaneurysm formation. The natural history of this entity is poorly defined, but most authors recommend repair. Techniques include primary closure of the ventricular defect and extensive repairs, as advocated for true ventricular aneurysm (see below).

# LEFT VENTRICULAR ANEURYSM

## Introduction

Although earlier reports had described enlargements of other cardiac chambers, the earliest reports of ventricular aneurysms found during autopsy were made by Galeati[509] and Hunter[510] in 1757.[511] Theories about their etiology abounded, but it was not until 1880 to 1900 that many authors independently recognized the correct relationship between coronary thrombosis, MI, ventricular scarring, and aneurysm formation.[511] The surgical correction of postinfarction ventricular aneurysm began with the use of a fascia lata graft by Beck in 1942.[512] Likoff and Bailey[513] reported the first successful aneurysm excision using a Satinsky clamp on a beating heart in 1955; that was followed by the work of Cooley and associates, who in 1958 performed the first modern aneurysm excision using CPB.[514] Since that time, repairs have been improved by a series of surgeons who have recognized the importance of normal ventricular geometry to ventricular function.[357,515–519]

Traditionally, LV aneurysm was defined as a region of myocardium exhibiting an abnormal diastolic contour with systolic dyskinesia and paradoxic bulging. However, growing experience with ventricular aneurysm as well as ischemic cardiomyopathy has led to the recognition that even large regions of akinesis without the traditional paradoxic systolic bulging can have deleterious effects on ventricular function (so-called functional aneurysm).[520] Several authors have proposed that any region of myocardial asynergy (akinesia or dyskinesia) large enough to reduce LV function be treated as an LV aneurysm.[521–523]

## Pathophysiology

The formation of LV aneuryms (whether traditional or functional) results from the remodeling process that occurs after transmural MI. This process has been divided arbitrarily into an early phase and a late phase. The early phase (less than 72 h after an infarct) is characterized by infarct expansion that may result in ventricular rupture or ventricular aneurysm.[524] The late phase (more than 72 h) involves global ventricular responses to changes in wall stress and strength, including chamber dilatation, mural hypertrophy, and changes in LV geometry that lead to poor contractile function.[525]

### EARLY REMODELING

Early remodeling results primarily from the effects of migration of inflammatory cells into the infarct zone. Necrotic myocytes initiate complement activation and free radical generation, which leads to a cytokine cascade and the migration of neutrophils into the infarct zone.[526] Neutrophil-mediated proteolysis leads to degradation of the intermyocyte collagen struts, resulting in infarct expansion within hours of infarction.[425,527]

The wall thinning and dilatation of infarct expansion lead to elevations in both diastolic and systolic wall stress (LaPlace effect). This causes a further increase in muscle fiber tension. Combined with the greater tendency for infarcted and ischemic myocytes to stretch under a constant load, progressive dilatation results until fibrosis and scarring supervene.[528] Deformation of the border zone and noninfarcted remote myocardium lead to alterations in Starling forces with adaptive changes in ventricular function, including augmented systolic shortening, activation of the sympathetic adrenergic system, and stimulation of natriuretic peptides.[525] When the region of viable myocardium is large enough, these mechanisms result in maintenance of cardiac output and systemic perfusion. However, in the longer term these mechanisms also result in the development of ventricular hypertrophy and higher myocardial oxygen demand in the remainder of the ventricle.

Infarct expansion occurs rapidly after MI. In more than 55 percent of cases, aneurysms are evident within 48 h; the remainder develop within the first 2 weeks.[520] This period forms the vulnerable period in which defects resulting from ventricular wall weakness (including rupture and aneurysm) are most likely to occur because the necrotic myocytes have not been replaced with scar. In cases in which viable, hibernating myocardium is present in the infarct zone, aneurysms seen on initial angiography may resolve over the course of several weeks.[529] Furthermore, reperfusion of the infarct zone may halt the remodeling process and prevent aneurysm formation, as reperfusion has been associated with a lower incidence of ventricular aneurysm.[529,530]

### LATE REMODELING

The late phase of remodeling in the setting of ventricular aneurysm is dominated by the response of the functioning myocardium to the presence of the aneurysm. During that time, the aneurysm becomes composed primarily of scar tissue. This leads to both systolic and diastolic dysfunction. During systole, the aneurysm fails to contract, leading to a reduced ejection fraction and cardiac output. In diastole, the aneurysm wall does not undergo normal distention, resulting in elevated LV diastolic pressure.

The normal myocardium attempts to compensate for these changes primarily with two mechanisms: myocyte hypertrophy and changes in ventricular geometry that attempt to redistribute the wall stress more evenly across the ventricle.[525] Reduction of ventricular wall stress with nitrates between 2 and 8 weeks after an infarct reduces hypertrophy,[531,532] and similar effects as well as decreased ventricular dilatation can be seen with ACE inhibitors.[533–535] Because these compensatory mechanisms may maintain cardiac output and coronary perfusion, ventricular aneurysms may remain asymptomatic for long periods. However, unless the aneurysm is small, progressive dilatation and hypertrophy ultimately result in increasing myocardial oxygen demand with progressive heart failure. The development of heart failure may occur (as it does in aortic regurgitation) with a sudden and profound presentation as the ventricle finally decompensates.[536,537]

## Clinical Features

The incidence of LV aneurysm depends on the definition and diagnostic techniques used, but approximately 10 to 35 percent of patients develop a region of systolic akinesia or dyskinesia after transmural MI.[511,520,538] Ninety percent of aneurysms occur on the anterior portion of the LV, approximately 25 percent of which occur near the apex.[539–541] Patients with ventricular aneurysm are more likely to have had a previous MI, to have a decreased ejection fraction (less than 50 percent), and to have increased LV end-diastolic pressure (LVEDP) (>21 mm Hg) compared with post-MI controls.[538]

Patients with ventricular aneurysm commonly present with CHF. Angina is also a common symptom, occurring in 44 to 98 percent of patients, usually related to obstruction of non-infarct-related arteries as oxygen demand in the dilated LV exceeds oxygen supply.[536,542,543] Other presenting symptoms include dyspnea and other symptoms of CHF as the LV decompensates and can no longer maintain the additional workload required to compensate for the aneurysm. Arrhythmias may occur in the scar tissue, leading to symptoms such as syncope, palpitations, and aggravation of angina or dypnea. Significant ventricular arrhythmias occur in 20 percent of large aneurysms but only 3 percent of smaller ones.[544] Finally, mural thrombus is found in 50 percent of patients undergoing surgery and is especially common in larger aneurysms.[511,536,545] Although this is rare, patients may present with symptoms of embolic disease, including stroke and peripheral arterial occlusion.

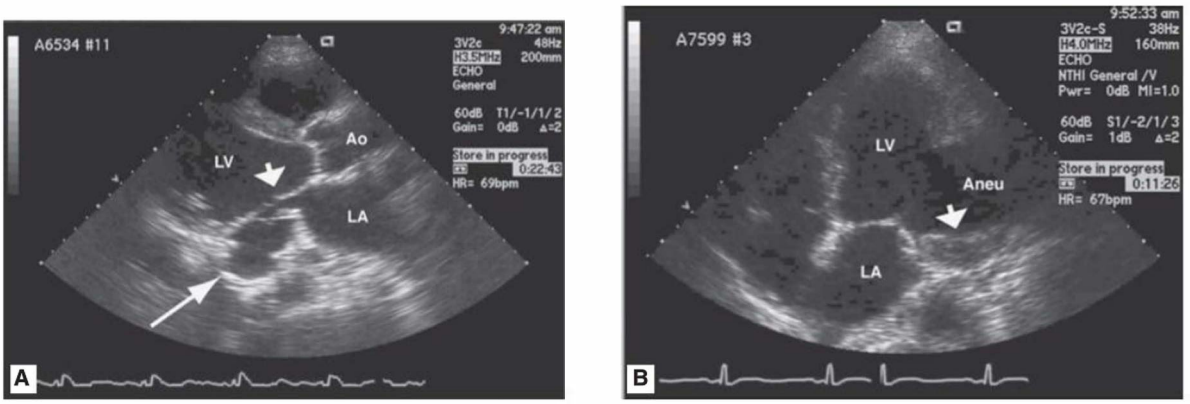



**FIGURE 31-24** Two-dimensional echocardiograms. **A.** Left ventricular pseudoaneurysm (*white arrow*) just inferior to the mitral valve annulus. The ventricular wall continues across the mouth of the pseudoaneurysm (*large white arrowheads*). Small white arrowhead indicates the mitral valve leaflets. **B.** In contrast, in a true left ventricular aneurysm, the ventricular wall forms the lateral margin of the aneurysm. Mural thrombus (*white arrowhead*) is visible along the aneurysm wall. Ao, aorta; MV, mitral valve; LV, left ventricle; LA, left atrium; PsA, pseudoaneurysm; Aneu, aneurysm.

## Diagnostic Modalities

Historically, electrocardiographic changes (Q waves and persistent ST changes in the anterior leads) and chest roentgenogram findings (LV enlargement and cardiomegaly) have been described in LV aneurysm, as have a variety of physical signs. However, these findings are not specific and play little role in the modern diagnosis of this disease.[511]

### ECHOCARDIOGRAPHY

Echocardiography is useful as a noninvasive test for mechanical complications in patients with coronary symptomatology and coronary artery disease. It can identify valvular disease, including MR, that may mimic the vague symptoms of ventricular aneurysm. In addition, it can differentiate true aneurysms from false aneurysms and evaluate for mural thrombus (Fig. 31-24).

### ANGIOGRAPHY AND VENTRICULOGRAPHY

Although echocardiography has advantages as a test that is noninvasive and easy to perform, ventriculography remains the gold standard for the diagnosis and preoperative evaluation of ventricular aneurysms (Fig. 31-25). In addition to defining cardiac function, it permits determination of coronary anatomy, allowing for optimal operative planning. Di Donato and associates[522] described a method for estimating LV aneurysm size accurately by using the centerline method. Previously, estimates of LV function and aneurysm size were made qualitatively by the cineangiographer. In their study, the extent of asynergy (A percent) was calculated as the percent length of the LV perimeter showing fractional shortening less than two standard deviations from the normal mean value. Surgical outcome correlated with A percent rather than with the presence or absence of dyskinetic motion.

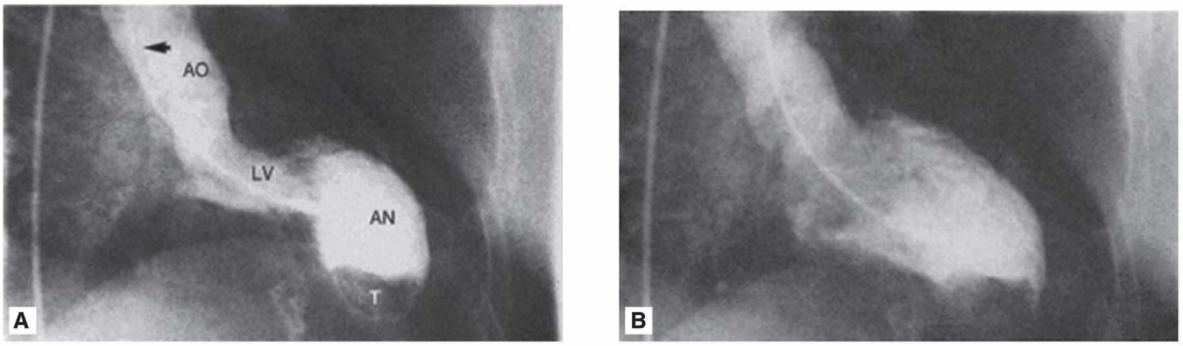



**FIGURE 31-25** Angiography of left ventricular aneurysm. The systolic image (**A**) clearly shows the large region of apical dyskinesia with mural thrombus, whereas the diastolic image (**B**) appears relatively normal. AN, aneurysm; LV, left ventricle; AO, aorta. (From Patel R, Shenoy MM. Images in clinical medicine: Left ventricular aneurysm. *N Engl J Med* 1993;329(4):246.)

### OTHER MODALITIES

Cardiacgated MRI provides highly accurate delineation of LV geometry and size and can identify mural thrombi. However, it cannot assess coronary anatomy or cardiac function adequately and therefore is not likely to supplant angiography in the near future.

## Medical Therapy

Medical therapy for LV aneurysm consists predominantly of agents directed at minimizing the deleterious aspects of LV remodeling. Nitrates have been shown to reduce myocyte hypertrophy but have not been shown to have a beneficial effect on mortality in clinical trials.[51,546] ACE inhibitors also may inhibit infarct expansion and reduce the incidence of aneurysm. Multiple studies have shown survival benefits in all patients with MI and in those with LV dysfunction.[51,546–548] Although studies have not addressed medical therapy for ventricular aneurysms specifically, standard treatments for LV dysfunction, including β-blockade and ACE inhibitors, should be used as indicated.

## Surgical Therapy

### INDICATIONS FOR OPERATIVE REPAIR

Many asymptomatic patients can be managed medically with excellent results. In 18 patients with asymptomatic ventricular aneurysms, Grodin and coworkers noted 90 percent survival at 10 years with a stable clinical course over that time; this contrasts with the 22 symptomatic patients who had 10-year survival below 50 percent.[549] However, the presence of an aneurysm involving more than 25 percent of the LV surface puts a significant strain on the remaining healthy myocardium.[536] In these circumstances it is likely that as with aortic regurgitation, a stable clinical course may be followed by abrupt decompensation with an abrupt increase in operative risk; these patients should receive operative therapy before decompensation.[536,550] However, small asymptomatic aneurysms in patients without elevated LVEDP and without the need for coronary revascularization may be managed medically. Frequent follow-up is important, as any deterioration in LV function or increase in aneurysm size should lead to surgical repair.[551] In addition, asymptomatic patients with comorbid conditions, including operative coronary artery disease and MV dysfunction, should be considered for concomitant aneurysm repair.[551]

Symptomatic patients should be evaluated for operative repair of a ventricular aneurysm; whether the aneurysm is primarily akinetic or dyskinetic, outcomes are similar.[522] Few aneurysms are too large for surgical repair. In the absence of involvement of the PMs, there is almost invariably enough ventricular muscle to sustain cardiac output.[536] Even when the contractile ejection fraction is between 0.25 and 0.30, aneurysms may be treated successfully with surgery provided that the mean pulmonary artery pressure is less than 40 mm Hg and the cardiac index is greater than 2.1 L/min; if these conditions are not met, the patient should be considered for transplantation, especially when RV dysfunction, permanent MR, and poor targets for coronary revascularization coexist.[536,544,550] Before surgery these patients should undergo right and left heart catheterization with delineation of the coronary anatomy. MR should be evaluated, and appropriate treatment planned.

### OPERATIVE TECHNIQUE

A median sternotomy is performed, saphenous vein or arterial conduits are harvested as needed, and the heart is cannulated for coronary bypass. Except in cases in which the right ventricle must be entered, a single two-stage right atrial cannula is usually sufficient. If indicated, epicardial mapping should be performed. To produce asystole and myocardial relaxation, most authors recommend cold anterograde cardioplegia with a solution containing potassium chloride.[551] A linear left ventriculotomy is then made approximately 3 to 4 cm lateral to the LAD. Mural thrombus then is removed, and blood is aspirated from the ventricle to identify positively the transition zone between viable myocardium and fibrotic scar. A variety of techniques have been described for repair of the LV after aneurysm excision.

***Plication.*** Plication consists of direct closure of the defect without aneurysm excision. Buttressed two-layer monofilament is used to plicate the scar and should be oriented to maintain normal LV geometry. It should be reserved for very small aneurysms without mural thrombus in cases in which LVEDP and LV function are largely preserved.[536]

***Linear Repair.*** In 1958, Cooley described the first successful aneurysmectomy using a linear repair with CPB. It remains a popular repair, although surgeons[551] increasingly are turning to a geometric repair (see below). A linear repair consists of excision of the aneurysm, leaving a 3-cm rim of scar tissue for fixation of the suture line. The defect then is closed with buttressed mattress sutures placed through the fibrous base. Although it is simple in concept and technique, this procedure leads to alterations in LV geometry that may have a significant impact on long-term function. In particular, the suture line approximates the lateral wall and medial (septal) wall of the LV at a point where they usually would be separated by at least a few centimeters, decreasing LV size and distorting LV geometry. Furthermore, there is no exclusion of septal paradox when the septum is involved in the scarred region.[536]

***Geometric Reconstructions.*** A number of surgeons noted high mortality after the linear repair and were troubled by the deformity in the ventricular cavity that resulted. Hutchins and Brawley[552] first brought significant attention to the problem of LV geometry after linear repair and recommended a repair described by Stoney and associates[515] in which the lateral myocardial wall was advanced down the septum to

create greater curvature and volume in the LV. Early attempts to ameliorate the problem of LV geometry after aneurysm resection included those of Daggett and associates,[357] who performed an external patch technique, and those of Komeda and associates,[553] who used an inverted T closure of the ventriculotomy to preserve the normal conical shape of the LV.

***Circular Patch Technique.*** The circular patch technique is most suitable for aneurysms of the posterior portion of the heart.[554] After debridement of the ventriculotomy rim and removal of thrombus, a Dacron patch is cut to a size 2 cm larger in diameter than the defect. Pledgeted 0 horizontal mattress sutures then are used to secure the patch, with the pledgets remaining outside the ventricular cavity. Hemostasis is obtained with a second layer of sutures as required.

***Endoventricular Patch Technique.*** Subsequently, Jatene,[555] Dor and colleagues,[523,556,557] and Cooley and coworkers[519] described techniques for ventricular reconstruction, all of which involve placement of an endocardial patch in an attempt to maintain normal LV and septal geometry. The technique advocated by Jatene involves the placement of a pursestring suture around the orifice of the aneurysm on a beating heart. Those sutures are used to bring the orifice down to a size estimated to be close to that of the original infarcted area.[536] If the aneurysm is small, it is possible simply to close the defect at this point (although this differs from a linear repair in that the pursestring brings the ventricular wall together with minimal alteration in geometry). More commonly, the aneurysm is resected and a patch is secured to the endoventricular side of the orifice. Although operating on a beating heart makes appropriate placement of the sutures easier, the large amount of prosthetic material left in contact with the pericardium increases the risk of postoperative infection and makes reoperation more difficult secondary to adhesions.[536]

Dor's technique involves slight modifications, including the invariable use of a patch for closure and extension of the patch to exclude scarred septum rather than septal plication as described by Jatene.[558] Finally, in the technique advocated by Cooley and coworkers, the sac is not excised but instead is sutured closed over the patch to augment hemostasis (Fig. 31-26).[519] The advantages of these techniques include applicability to early aneurysms when infarct tissue is friable, preservation of the LAD, and separation of prosthetic material from the sternum when the aneurysmal sac is closed over the defect. In addition, these techniques facilitate patching of infarcted interventricular septum. Recently, Alonni and associates published excellent results with endoaneurysm repair via port access surgery in seven patients.[559]

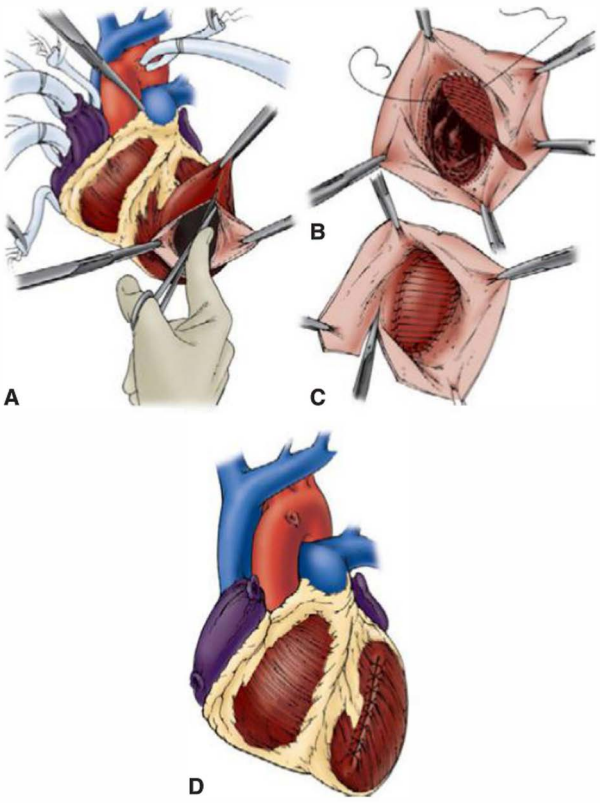



**FIGURE 31-26** Endoaneurysmorrhaphy as advocated by Cooley and associates. (Adapted from Cooley DA, Frazier OH, Duncan JM, et al. Intracavitary repair of ventricular aneurysm and regional dyskinesia. *Ann Surg* 1992;215(5):417–423.)

## CONCOMITANT PROCEDURES

Valve surgery should be performed in patients with MV disease. Repair or replacement can be performed via the ventriculotomy or by using a standard left atriotomy. Preoperative catheterization should identify patients who require concomitant CABG. Complete myocardial revascularization should be performed if possible. In patients undergoing linear repairs, the distal LAD generally is occluded by the repair. If patients have adequate distal targets, bypass may be performed, although most of these patients have significant distal disease, making bypass impossible.

## OTHER TECHNIQUES

The injection of a variety of stem cells (including fetal smooth muscle cells and bone marrow cells), as well as autotransplantation of healthy cardiomyocytes, has been reported to improve cardiac function and prevent LV dilatation in animal models.[560–563] This work has been extended to the use of bioengineered vascular smooth muscle grafts during endoventricular aneurysm repair.[564] Although experimental, this work holds promise for providing short-term recovery of normal LV geometry and preventing long-term deleterious LV remodeling.

## POSTOPERATIVE CONSIDERATIONS

Postoperatively, patients frequently require inotropic support to facilitate weaning from CPB. Dopamine may be

particularly useful for its inotropic and chronotropic effects. Abnormal ventricular compliance and an increased risk for postoperative ventricular arrhythmias in this population may decrease the effectiveness and increase the risk of higher doses of inotropes. Low-level resting tachycardia (heart rate between 100 and 120) may be required to maintain the cardiac index. If pharmacologic agents are ineffective, an IABP may be required in the short term.

## Outcomes and Prognosis

### EARLY RESULTS

Operative mortality in recent series of both linear repair and ventricular reconstruction procedures are approximately 2 to 13 percent, with most series at the lower end.[536,539,553,565–568] Multiple authors have sought to compare linear repair and ventricular reconstruction techniques; although no one has used a randomized trial, most results suggest that ventricular reconstruction provides improved results.[522,566,569,570] In a recent study of 149 patients operated on for LV aneurysm, Lundblad and associates found linear repair to be an independent predictor of both early and overall mortality (odds ratio 4.4, 95 percent CI 1.0–16.0).[566]

Other risk factors for early mortality include advanced age,[553,566] three-vessel coronary disease,[566] previous coronary artery bypass,[553] emergency operation,[566] poor preoperative ejection fraction (<0.20),[522,553] preoperative severe heart failure (NYHA class IV),[522,553,566,571] nonuse of the IMA,[522,571] MR,[522] and a history of malignant ventricular arrhythmias.[566] Cardiac failure constitutes the most common cause of postoperative death,[567] but ventricular arrhythmias and multiorgan system failure are also important.[567]

### LATE RESULTS

Long-term mortality also appears to be improved with the use of ventricular reconstruction vs linear repair.[566] Five-year mortality varies from 20 to 42 percent.[539,566,572–574] Ten-year survival is only approximately 30 percent[567,572]; however, survival in medical patients is probably worse, and although medical treatment of heart failure has improved, the mechanical dysfunction at the heart of ventricular aneurysm still must be addressed.[575] Most of these patients die of progressive heart failure or recurrent MI or experience sudden death.[567] Risk factors for long-term mortality are advanced age,[566] three-vessel disease,[566] low LVEF or preoperative heart failure,[539,566,567] high PCWP,[567] use of an IABP,[567] more than one previous MI,[566] 2+ or 3+ MR,[539] and a history of malignant ventricular arrhythmia.[539,566]

### LEFT VENTRICULAR FUNCTION

Most measures of LV function are improved after linear repair or ventricular reconstruction. The large study by Di Donato and colleagues demonstrated a significant increase in LVEF after surgery (from 36 to 50 percent) with decreased pulmonary pressures and end-diastolic volume index (EDVI).[522] Even patients with large akinetic scars (who had the worst preoperative function) benefited significantly (ejection fraction increased from 25 to 41 percent).[522] Similar improvements in LVEF,[539,573,576,577] left ventricular end-diastolic volume (LVEDV),[576] myocardial oxygen consumption,[577] and exercise tolerance[519,576] have been reported by others regardless of the technique used.

There is continuing controversy about the relative advantages of linear repair and ventricular reconstruction. No randomized data exist, and the retrospective data are plagued by problems of comparisons across different time periods, surgeons, and patient populations. Several experienced groups have published large series reporting improvement in postoperative function with the switch to ventricular reconstruction techniques.[540,541,578–580] However, other groups have reported no difference, and some have reported an increase in operative mortality.[570,581,582] It appears that acceptable results can be obtained with either technique, and the most important determinant of improvement in LV function may be the appropriate size of the LV cavity rather than the specific technique used.[540,552,583] The persistence of improvements in LV function over the long term has not been studied extensively, but in humans only mild worsening of hemodynamic variables and cardiac function has been noted 7 years after surgery.[584] This suggests that although mortality remains high, it may result more from baseline coronary disease than from worsening pump function.

## Summary

Ventricular aneurysms result from regions of infarcted myocardium that are either akinetic or dyskinetic. This has profound effects on ventricular remodeling and in most patients results in progressive heart failure in the long term. Most aneurysms develop within 2 weeks of the inciting MI, and approximately 10 to 35 percent of patients develop an aneurysm after transmural MI. Most patients present with CHF, and the gold standard for evaluation remains angiography and ventriculography; this allows for evaluation of coronary disease and optimal operative planning. Patients with asymptomatic aneurysms may be managed medically, but those with symptoms or with extremely large aneurysms (more than 25 percent of LV surface) merit operative repair. Multiple techniques for repair have been described. The most commonly used in the modern era is a geometric repair with a patch closure of the site of aneurysm resection, optimizing LV geometry and minimizing long-term alterations in LV function. Operative mortality is approximately 10 percent, and 5-year mortality ranges from 20 to 42 percent. However, most patients have significant improvements in LV function and clinical status after aneurysm resection, and the high long-term mortality probably is related to the baseline medical condition rather than failure of the surgical repair.

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## MECHANICAL COMPLICATIONS OF MYOCARDIAL INFARCTION BOARD REVIEW QUESTIONS (CHAPTER 31)

1. What are the current American College of Cardiology/American Heart Association Guidelines Committee recommendations for initial reperfusion therapy in patients with three-vessel coronary disease in cardiogenic shock from AMI:
   A. Placement of DES
   B. Placement of bare metal stents
   C. CABG
   D. Balloon angioplasty
   E. No intervention

2. A 45-year-old man with a history of medically managed multivessel coronary disease presents with a new ST-elevation myocardial infarction. Approximately 7 days after his myocardial infarction, he complains of severe dyspnea. His chest x-ray demonstrates severe bilateral pulmonary edema. Physical exam is significant for a mild holosystolic murmur. Which of the following complications of myocardial infarction is he most likely to have:

   A. PM rupture
   B. VSR
   C. Ventricular free wall rupture
   D. Ventricular aneurysm
   E. Ventricular dysfunction due to myocardial stunning

3. Which of the following patients would be most at risk for VSR following myocardial infarction:

   A. A 40-year-old with a history of angina with stenoses in the LAD (80 percent), RCA (95 percent), and circumflex (80 percent), 1 week following myocardial infarction
   B. An 85-year-old without past medical history with a 90 percent LAD stenosis, 24 h following myocardial infarction
   C. An 85-year-old with a history of two previous myocardial infarctions who has a 95 percent LAD stenosis, 85 percent RCA stenosis and two marginal branches with 90-and 95 percent stenoses, 72 h following myocardial infarction
   D. A 60-year-old without past medical history with a 90 percent LAD lesion, 2 weeks following myocardial infarction
   E. An 85-year-old without past medical history with a 95 percent occlusion of the RCA, 24 h after myocardial infarction

4. A patient who is 7 days out from a large anterior wall infarction develops sudden onset of chest pain and dyspnea. Chest x-ray demonstates small bilateral pleural effusions. Echocardiography reveals a large pericardial effusion with evidence of intrapericardial blood clots. There is no evidence of MR or left-to-right shunting across the ventricular septum. At this point the patient has a heart rate of 120, blood pressure is 75/60, respiratory rate of 12. The next most appropriate intervention is:

   A. Percutaneous coronary intervention
   B. Transfer to the operating room
   C. Pericardiocentesis
   D. Placement of a tube thoracostomy
   E. Placement of an IABP

5. In patients with ventricular aneurysms, all of the following are indications for repair, EXCEPT:

   A. Symptoms of CHF
   B. Decreased LVEF <40 percent
   C. Embolic stroke in the setting of a left ventriular thrombus
   D. Increase in aneurysm size
   E. Aneurysm exceeding 15 percent of the LV surface

## ANSWERS

1. **Answer: C.** Coronary artery bypass grafting is the recommended treatment for three-vessel coronary disease and cardiogenic shock in the setting of acute myocardial infarction.
2. **Answer: A.** A patient with new-onset pulmonary edema following myocardial infarction is most likely suffering from acute MR. The murmur of MR may be subtle on physical exam. Seven days after infarction, acute onset of MR is most likely due to PM rupture, as ventricular dysfunction due to myocardial stunning should be improving rather than becoming acutely worse.
3. **Answer: B.** Risk factors for VSR include older age and a lack of previous history of angina or MI. In addition, single-vessel coronary disease is more common among patients with VSR. VSR most commonly occurs in the early post-MI period within 24 to 48 h.
4. **Answer: C.** This patient is at high risk for having a ventricular free wall rupture. While immediate operative repair of free wall rupture is indicated, only appoximately 70 percent of patients with these echocardiography findings will have a free-wall rupture. More importantly, the patient is decompensating from cardiac tamponade and needs immediate therapy to relieve the pericardial effusion. Pericardiocentesis will both treat the tamponade and enable diagnosis of the source of the effusion to direct further therapy.
5. **Answer: E.** Asymptomatic patients with small aneurysms may be managed medically with good long-term results. However, the development of symptoms (whether due directly to ventricular dysfunction or secondary processes such as embolic disease) merits operative evaluation. Also, increasing aneurysm size or decreasing ventricular function should prompt operative repair.

# 32 Aortic Valve Replacement

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## KEY CONCEPTS

- Epidemiology
  - Approximately 100,000 aortic valve replacement procedures have been performed in the United States in the last 10 years. Most patients present with aortic valve pathology that requires replacement between ages 60 and 80. Replacement for aortic stenosis is performed much more commonly (85 percent) than is replacement for aortic insufficiency.
- Pathophysiology
  - With aortic stenosis, there is a decrease in the effective valve orifice area, resulting in progressive obstruction of the left ventricle. The ventricle adapts through concentric hypertrophy, which increases diastolic stiffness and impairs the efficacy of diastolic coronary blood flow. Diastolic dysfunction precedes systolic dysfunction. With aortic insufficiency, gradual ventricular dilatation occurs, causing an increase in wall stress. This, in conjunction with the decrease in diastolic pressure, reduces diastolic coronary blood flow. With continued dilatation, fibrosis occurs, increasing ventricular stiffness and impairing diastolic relaxation. Eventually, the preload reserve of the ventricle is reached and further dilatation and fibrosis result in a decline in systolic function that may not be recoverable after aortic valve replacement.
- Clinical features
  - Aortic stenosis patients complain of combinations of symptoms of chest pain, syncope, and congestive heart failure. The life expectancy of patients with untreated aortic stenosis who present with angina is 50 percent at 5 years, 50 percent at 3 years with syncope, and 50 percent at 2 years with congestive heart failure symptoms. A small proportion of patients with aortic stenosis present with sudden death. Aortic insufficiency has a more insidious onset and usually is characterized by the development of slow congestive heart failure and fatigue symptoms. Angina pectoris and syncope are rare in these patients. These patients may be managed on medical therapy for protracted periods with an acceptable quality of life.
- Diagnostics
  - The work-up for candidates for aortic valve replacement includes echocardiography to estimate ventricular function and the degree of stenosis or insufficiency and cardiac catheterization to measure cardiac output, calculate aortic valve area, and image the coronary arteries for significant lesions. A careful oral examination or dental consultation is very important to prevent postoperative prosthetic valve infection.
- Treatment
  - Aortic valve replacement options include homograft, stented and stentless xenograft tissue, and mechanical valves. The decision to use each of these is dependent on patient age and valve preference, comorbid conditions, and contraindications to the use of anticoagulants. A variety of options are available to manage potential patient–prosthesis mismatch at the time of surgery.
- Outcomes
  - The outcomes of tissue valve replacement show 80 to 93 percent freedom from structural valve failure at 10 to 14 years. Bleeding and thromboembolic events complicate mechanical valve replacement at a rate of approximately 4 percent per patient-year. Homograft valve replacements have the highest freedom from structural valve deterioration, with rates of 81 to 93 percent at 15 years. Survival after aortic valve replacement is dependent more on patient comorbidities than on the requirement for valve replacement. Postoperative complications specific for aortic valve replacement include complete heart block (1 percent) and perivalvular leaks (1–2 percent).

## HISTORICAL BACKGROUND

### Aortic Valvotomy

The first attempt to open a stenotic aortic valve in a patient was performed by Theodore Tuffier on July 13, 1912.[1] This effort was accomplished by invaginating the ascending aortic wall with a finger and pushing the aorta through the valve. The 26-year-old male patient recovered and returned to his home in Belgium. Russell Brock dilated calcified aortic valves in humans in the late 1940s with instruments passed from the innominate artery or other arterial sources.[2] His results were initially poor, and he[3] as well as Bailey et al.[4] later used different dilators in various approaches with somewhat better results. However, the mortality for these patients remained high. Horace Smithy, a South Carolina surgeon, suffered from severe rheumatic aortic stenosis (AS). Having achieved national acclaim for the development and successful use of a valvulotome for closed commissurotomy in patients with rheumatic mitral disease, he developed an aortic valvulotome[5] and enlisted Dr. Alfred Blalock to perform the operation on him. Dr. Blalock agreed provided that he and Dr. Smithy perform the procedure together on another patient first. A patient was scheduled but unfortunately that patient died of ventricular fibrillation during induction of anesthesia. Shortly thereafter, Dr. Smithy died of complications related to his own severely stenotic aortic valve before the operation could be carried out.

### Mechanical Prostheses

In the early 1950s, Hufnagel[6] and Campbell[7] independently developed and implanted artificial valves in the descending thoracic aorta of dogs. In his paper published in 1954, Hufnagel reported a series of 23 patients starting in September of 1952 who had this operation for aortic insufficiency (AI).[8] These efforts preceded the evolution of the most successful of the caged ball valves, the Starr–Edwards prosthesis. This valve, created by M. Lowell Edwards, a retired engineer, and Albert Starr, a cardiac surgeon in Portland, OR, was originally implanted in the mitral position in August of 1960. The first clinical Starr–Edwards aortic valve implantation was performed in September of 1961.[9] Shortly after the introduction of the cage ball concept, a number of similar designs appeared in clinical use, which are beyond the scope of this chapter. However, excellent reviews are available.[9,10]

The concept of the tilting disc valve arose out of the concerns that cage ball valves were bulky and that the hemodynamics achieved were less than ideal. In an attempt to reduce the profile of these valves, a flat disc instead of a ball was used as an occluder. The earliest examples of the tilting disc concept were flat valves. These had a ring with a straight segment on which a disc was hinged much like the lid of a toilet seat. Other modifications included free-floating, polypropylene discs such as that introduced by Melrose and colleagues,[11] and other interesting designs such as those produced by Water and McLeod in Edinburgh.[12] In 1969, Bjork and Shiley produced a valve in which a free-floating disc was restrained by two low-profile M-shaped struts.[13,14] The first implantation of the Bjork–Shiley prosthesis was in 1975. In 1978, the disc profile was changed from plano-convex to convexo-concave (C-C model) and struts were modified such that the disc moved 2.5 mm downstream as it tilted.[14] In 1981, the valve ring was altered and a single heavier hook replaced the outlet strut, all of which was machined from one piece of metal with no welds (the monostrut valve).[15] Other examples of tilting discs valves included the Lillehei–Caster, Omniscience, and Omni Carbon valves. Some were removed from use because of the high incidence of thrombotic obstruction,[16] and others such as the Medtronic-Hall D16 Valve and the Bjork–Shiley C-C valves because of an unacceptable incidence of strut fractures.[17]

The earliest bileaflet mechanical valve designs were introduced by Gott and Daggett,[18] Kalke and Lillehei,[19] and Wada[20] in the early- to mid-1960s. These prostheses failed due to mechanical malfunctions and high thrombogenicity. However, from these failures arose the realization that bileaflet prostheses had hemodynamic characteristics superior to that of all of the prostheses available at the time. In 1976, the bileaflet design was modified and manufactured entirely from pyrolytic carbon.[21] Subsequent studies showed that the bileaflet design was very durable and that in addition, pyrolytic carbon was quite biocompatible and thromboresistant. The prototype pyrolytic carbon bileaflet valve, the St. Jude Medical Prosthesis, was first implanted clinically in 1977.[22] This valve has undergone a number of modifications since the original standard St. Jude valve was introduced including the lower profile Hemodynamic Plus (HP) Valve,[22] the Masters Valve (which allows internal rotation of the leaflets to get a better seating once the valve is implanted),[23] and the Regent Valve (with a modified external profile to create an even larger internal orifice area per valve size).[24] Other bileaflet valves are currently in use, such as the Carbomedics[25] (released for clinical use in December, 1986) and Sorin Bicarbon (released in 1990) models.[26]

### Bioprostheses

With the introduction of glutaraldehyde for the fixation of biological tissue by Carpentier and colleagues in 1969,[27] the use of bioprosthetic material, both porcine valves and bovine pericardium, became feasible alternatives to mechanical designs for valve replacement. The University of Padua has the most extensive experience with the Hancock standard porcine bioprosthesis, which was first clinically implanted in the aortic position in March of 1970.[28] The Hancock modified orifice (MO) valve was introduced in the wake of concerns about high postimplantation gradients with small valve sizes in the aortic position. This problem, due to the bulky muscle bar under the right coronary cusp of the valve, was reconciled with the MO design, a composite

valve that replaces the right coronary cusp with a cusp from another valve that does not contain the muscle bar. The Carpentier–Edwards standard porcine bioprosthesis was introduced in 1975.[29] Second-generation bioprostheses include the Carpentier–Edwards supra annular (SAV) porcine bioprosthesis, available since 1981,[30] the Hancock II porcine bioprosthesis, which was introduced in 1982,[31] and the Medtronic intact porcine bioprosthesis available since 1985.[32] In general, these valves offer improved zero-pressure fixation that preserves subtle but important histological features of the valve leaflets, and antimineralization treatments to reduce calcific degeneration of the valve tissue. In addition, more flexible, lower profile stent materials and reduced sewing rings are employed to create a larger effective orifice area (EOA). Numerous other porcine bioprosthesis are under evaluation.

The first bovine pericardial bioprosthesis was the Ionescu–Shiley valve developed by Marian I. Ionescu and G. Wooler in 1971.[33] In 1981, a low-profile model was released, but had a much higher rate of failure than the standard Ionescu valve. A final model III was implanted and used clinically before Shiley decided to cease the production of pericardial valves in October of 1977.[34] The Mitroflow pericardial valve was designed by Siegel and Totten and first clinically implanted in 1982.[35] The most common currently used pericardial valve, the Carpentier–Edwards pericardial valve, was first clinically implanted in Paris, France, in July 1980.[36] This valve has undergone a number of modifications, including the Perimount RSR[37] and Magna series.

The first clinically applicable bioprosthetic stentless aortic valve was the Toronto stentless porcine valve (SPV) as introduced by Dr. Tirone David at the University of Toronto in 1991.[38] This valve offered an increased EOA of the valve by minimizing sewing ring and eliminating the supporting struts. The stentless valve design consisted of a native porcine valve reinforced by a small amount of fabric sewn to the patient's annulus in a planar fashion followed by implantation of a small amount of porcine aorta around the valve commissures directly to the patient's own native aorta. Other stentless valves currently in use include the Medtronic free-style porcine prosthesis[39] and the Edwards Prima Plus porcine prosthesis.[40] Other stentless valves, such as the ATS-3F Therapeutics stentless equine bioprosthesis,[41] have been evaluated in clinical trials and are available for clinical use.

The first experimental animal studies involving homograft aortic tissue were performed by Lamb et al. in 1952, who implanted an allograft aortic valve into the descending aorta of the dog.[42] This was followed within 3 years of the clinical reimplantation of the allograft aortic valve into the human descending aorta by Murray[43] and subsequently by Heimbecker and associates in Toronto.[44] The technique for subcoronary implantation of allograft tissue using the single suture method was reported by Duran and Gunning in 1962[45] and implemented the same year by Donald Ross[46] in patients with a freeze-dried aortic valve, a feat performed shortly thereafter by Barrett–Boyes.[47] Sterilization of homograft valves has undergone a number of changes from formaldehyde, chlorhexidine, propiolactone, methylene oxide, gamma radiation, and storage using a carbon dioxide freezer at –70°C. Currently, most homograft valves are cryopreserved with low-dose antibiotics.

## EMBRYOLOGY AND ANATOMY

The aortic valve develops from three swellings or ridges of endomyocardial tissue at the proximal orifice of the septating truncus arteriosus. These ridges become hollowed out and reshaped to form three thin-walled cusps or pockets at approximately the sixth to seventh week of development.[48] The three aortic valve cusps are semilunar in shape and are named depending on whether or not the sinuses they subtend give rise to coronary artery ostia. Therefore, a right and a left coronary aortic cusp and one noncoronary cusp exist. The base (semilunar point of attachment to the aorta) of the leaflet is approximately one and a half times as long as its free margin. Portions of the noncoronary and a portion of the left coronary cusps are in continuity with the anterior leaflet of the mitral valve (the aorto-mitral continuity), which is an anatomical consideration that can become very important in the case of valve replacement for endocarditis. The aortic valve annulus is variable in its definition but is toughest in approximately the noncoronary section, constituting tissue between the left and right fibrous trigones of the heart. The ascent of the aortic attachment of the noncoronary cusp toward the right coronary/noncoronary commissure lies directly over the atrioventricular conduction system, which sits in the right fibrous trigone or central fibrous body of the heart. Sutures placed too deeply in this area during valve replacement will result in atrioventricular conduction block. It is important to understand that the aortic valve leaflets are attached to the aortic root in a scalloped fashion. Most techniques of valve replacement involve conversion of this scalloped aortic annulus to a relatively planar orientation, which can have important anatomic considerations. Certain stented bioprostheses are designed to maintain some of the scalloped architecture when implanted. Each aortic valve leaflet has a small nodular excrescence at its midportion called the node of Arantius or the nodulus Arantii.[49]

An aortic valve leaflet has three layers: the fibrosa or arteriosa (arterial side), the spongiosa (middle), and the ventricularis (ventricular side). These layers are composed of varying proportions of elastin, collagen and glycosaminoglycans. The outer layers of the valve cusps are covered in endothelial cells oriented perpendicular to the direction of blood flow.[50]

## ETIOLOGY AND PATHOPHYSIOLOGY

Aortic valve replacement (AVR) is performed in patients in whom there is an underlying morphologic or anatomic abnormality of the aortic valve independent of its

supporting structures, which causes it to become stenotic or regurgitant.

## Aortic Stenosis

AS typically arises as a result of degenerative calcification in the elderly or as a result of rheumatic degeneration in those individuals that have a history of rheumatic fever. Certain congenital conditions also predispose to AS. The most common of these is congenital bicuspid aortic valves, which occur in approximately 5 percent of the population.[49] It is believed that bicuspid aortic valves create abnormally turbulent flow during systole, which in turn causes recession of the leaflet intimal lining and predisposes the valve to calcification and development of stenosis. Irrespective of the cause, failure of the aortic valve to open completely subjects the left ventricle to a persistent and abnormally high pressure load that results in the manifestation of two distinct processes.[51–53] The first process is adaptive and is characterized by left ventricular (LV) hypertrophy aimed at off-setting the inciting pressure overload while the second process is maladaptive and is associated with continued myocyte hypertrophy in combination with progressive myocardial fibrosis, a process known to reduce ventricular compliance and to contribute to impairments in diastolic filling.[52,54–59] As LV wall thickness increases, further reductions in diastolic compliance are observed, the efficacy of diastolic coronary blood flow is impaired, and coronary flow reserve is reduced in the setting of increased oxygen requirements by the larger cardiomyocyte mass. As a result of these responses, patients may actually suffer from heart failure symptoms in the absence of overt LV systolic dysfunction. Without appropriate and timely surgical intervention, chronic LV pressure overload secondary to AS, with the attendant signs and symptoms of diastolic dysfunction, can progress to frank systolic heart dysfunction, a particularly ominous condition. In addition, severe ventricular hypertrophy may create intracavitary gradients proximal to the valve, which further compound ventricular unloading and that may not be correctable with AVR.

The effects of aortic valve stenosis on myocardial structure and function, prior to, and following AVR, have been extensively chronicled.[55–57] Krayenbeuhl and colleagues examined patients with AS prior to AVR and established that patients with AS exhibited significant increases in myocyte diameter and interstitial fibrosis compared to control patients while Villari and associates reported that LV relaxation was significantly prolonged prior to surgical correction.[56,57] These investigations linked changes within the cellular and extracellular compartments with the clinical syndrome of pressure overload induced diastolic dysfunction. Moreover, they also demonstrated that corrective surgery abolished many of these preoperative characteristics though to different degrees and over variable time courses.[55] Importantly, these investigations demonstrated that pressure overload induced abnormalities within the myocardium persist years beyond surgical correction.

## Aortic Insufficiency

Isolated AI usually resolves as a consequence of structural abnormalities of the aortic valve, causing leaflet elongation and prolapse as seen with myxomatous degeneration or in various connective tissue disorders such as Marfan syndrome. Other causes include infective endocarditis, traumatic disruption of a valve leaflet from severe acceleration/deceleration injuries, rheumatoid arthritis, Reiter's syndrome, ankylosing spondylitis, psoriasis, and Takayatsu's disease. Patients with calcified degenerative aortic valves may undergo leaflet perforation or tearing, especially in the belly of the leaflet, which results in combined stenosis/regurgitation.

Acute severe incompetence of the aortic valve causes a large volume of diastolic flow reversal into the left ventricle. The ventricle does not have time to adapt to this sudden event and a rapid rise in diastolic pressure occurs, causing the pulse pressure to decrease forcing early mitral valve closure to prevent back flow into the left atrium. There is a concomitant increase in heart rate and a decrease in cardiac output. The result is a rapid onset of congestive heart failure.

Chronic, progressive valve incompetence allows time for the accommodation of a smaller gradation in flow reversal. Thus, gradual ventricular dilatation occurs, with preservation of diastolic compliance such that end-diastolic pressure is not elevated in well-compensated AI. The enlarging ventricular chamber causes an increase in wall stress (as an extension of Laplace law), which will result in some ventricular hypertrophy, but overall the chamber diameter to wall thickness ratio continues to increase. The preceding events, in conjunction with the decrease in diastolic pressure, will reduce diastolic coronary blood flow. With continued dilatation, fibrosis occurs, which increases ventricular stiffness further and impairs diastolic relaxation. Eventually, the preload reserve of the ventricle is reached and further dilatation and fibrosis result in a decline in systolic function, which may not be recoverable with AVR.

# CLINICAL FEATURES

## Aortic Stenosis

Patients with AS typically present to physicians in their 60s and 70s. Patients complain of combinations of symptoms composing the classic triad of chest pain, syncope, and congestive heart failure. Chest pains in the form of classic angina pectoris are the initial symptom in 50 to 70 percent of patients. Syncope is the presenting symptom in 15 to 30 percent of patients. The life expectancy of untreated AS in patients presenting with angina is 50 percent at 5 years, 50 percent at 3 years with syncope, and 50 percent at 2 years with congestive failure symptoms such as exertional dyspnea, peripheral edema, orthopnea, and paroxysmal nocturnal dyspnea.[60] A small proportion of patients with AS present with sudden death, most likely due to life-threatening arrhythmias

resulting from severe LV hypertrophy. However, this seldom occurs in patients who have not had antecedent symptoms. In patients who have congenital conditions predisposing to AS, such as congenital bicuspid aortic valves, presentation may occur 10 to 15 years earlier.

## Aortic Insufficiency

AI has a more insidious onset and is usually characterized by the development of slow congestive heart failure and fatigue symptoms.[61] Angina pectoris and syncope is rare. The patients may be managed on medical therapy for protracted periods of time with an acceptable quality of life. It is possible (but becoming less common) for patients with AI to be managed nonoperatively to the point where the myocardium is so decompensated that surgical treatment becomes untenable.

# DIAGNOSTIC MODALITIES

## Physical Examination

### AORTIC STENOSIS

Patients with AS present with a typical murmur, which consists of a blowing crescendo–decrescendo type pattern best heard in the left sternal border with radiation to both carotid arteries. The heart is hypertrophied but not enlarged, so typically patients do not have palpable enlarged hearts with this condition. Palpation of the pulse reveals low volume and a delayed upstroke (*pulsus parvus et tardus*), owing to the gradual severity of the stenosis.

### AORTIC INSUFFICIENCY

With AI, gradual LV dilatation is observed. On cardiac auscultation, an early diastolic murmur radiates to the point of maximal intensity (apex), and may be associated with a mid-diastolic murmur caused by fluttering of the anterior mitral valve leaflet (Austin–Flint murmur). In addition, a number of interesting physical exam signs have been noted in these patients, including "water-hammer" (Corrigan) pulses with wide pulse pressures and low diastolic pressure, DeMusset's sign (bobbing of the head), Muller's sign (wobbling of the uvula), pistol shots, Durozier's sign (murmur heard over the femoral arteries), and Quinke's sign (cyclical blanching of the nail beds).

An extremely important aspect of the physical examination in patients being considered for aortic valve surgery is the examination of the mouth and teeth. Dental disease is a major cause of prosthetic valve endocarditis (PVE) and no AVR, unless under extremely urgent circumstances, should be performed without having appropriate dental clearance when deemed necessary.

AS and AI are not associated with any specific serum laboratory abnormalities.

## Diagnostic Studies

### AORTIC STENOSIS

The chest radiograph shows calcification of the aortic valve, and a subtle convexity of the LV silhouette due to LV hypertrophy. The electrocardiogram shows LV hypertrophy, and left or right bundle branch block if the calcific process causing stenosis involves the conduction system significantly. Transthoracic echocardiography shows the calcified valve with poorly mobile leaflets in the parasternal long-axis view. A short-axis view of the valve may show whether the valve is bi- or tricuspid. Continuous-wave Doppler is used to calculate valve gradients and valve area. The peak valve gradient is calculated as a function of the highest measured flow velocity (defined as peak gradient = $4V^2$, where $V$ = velocity), which is often demonstrated in the four-chamber view. The mean gradient is calculated as a function of the area of the continuous wave flow velocity curve. Valve area is calculated by the continuity equation and utilizes both continuous wave- and pulse wave Doppler. The calculation entails multiplying the LV outflow tract (LVOT) area by the LVOT flow velocity as measured by pulse-wave Doppler and then dividing the derived value by the continuous wave velocity. The accuracy of echocardiographic measurements is confounded by the presence of extensive calcification, basal septal hypertrophy, and probe orientation. In addition to the above, severe LV hypertrophy may manifest with subvalvular, intracavitary gradients. If present, this may present a significant challenge to the surgeon at operation.

At catheterization, aortic valve area is estimated at cardiac catheterization using the Gorlin formula, which, in the simplified version, is defined as valve area = cardiac output/gradient$^{-2}$.[62,63] A caveat to the Gorlin equation is that it is very sensitive to flow. Therefore, patients who have reduced ejection fraction may have a falsely reduced valve area, as calculated by the Gorlin equation. In these cases, correlation to the echocardiographic calculation is helpful.

### AORTIC INSUFFICIENCY

The degree of AI can be estimated by echocardiography, where the rapidity of equilibration of aortic and LV diastolic pressure determines the degree of insufficiency. Accordingly, a diastolic pressure half-time of <300 ms, a short mitral deceleration time (<150 ms), and premature closure of the mitral valve all indicate severe AI. LV cavity dilatation is also assessed.

At catheterization, the degree of AI can be estimated by the degree of leakage of contrast into the left ventricle during diastole. However, this estimation is relied upon less frequently in lieu of the echocardiographic methods described above.

Patients with AS and AI should be initially evaluated with a transthoracic echo. If transthoracic echocardiography confirms the suspected diagnosis and the patient's symptoms warrant operation, it is logical to proceed with coronary catheterization to exclude the presence of coronary artery

disease (CAD). In females less than 40 years of age and males less than 35 years of age with no cardiac risk factors, coronary catheterization can be omitted relatively safely.

## MEDICAL (NON SURGICAL) THERAPY

### Aortic Stenosis

There is no acceptable medical therapy for symptomatic AS. The use of antihypertensive medications and angiotensin converting enzymes inhibitors must be carried out with caution because of the risk of profound hypoperfusion. Use of beta-blockade may slow the heart rate and provide for a longer systolic interval potentially resulting in higher stroke volume in patients with stenotic valves. Digitalis glycosides may provide a mild positive inotropic effect, which may be of benefit. Percutaneous valvotomy[64] will reduce a tight stenosis to moderate stenosis with a final valve area between 0.7 and 1.1 $cm^2$, still inferior to the valve area obtained with a prosthetic valve replacement, which usually provides a valve area over 1.5 $cm^2$. The hospital mortality associated with this procedure varies from 3.5 to 13.5 percent, and within 24 h 20 to 25 percent of the patients have at least one serious complication, in particular vascular complications at the puncture site. Despite a relatively modest improvement in valve function, the quality of life benefit rarely lasts beyond a year. This technique is useful for improving the clinical status of patients with severe AS as a preamble to conventional valve replacement.[65] Without valve replacement, however, the prognosis is poor. Currently, it is generally felt that valvotomy alone does not change the natural course of the disease. The poor midterm results are mainly due to the clinical status of the patients and to the moderate and transient improvement in valve function obtained by valvotomy.[66] More recently, and as discussed below, percutaneous valve deployment has been successfully employed in patients deemed too high-risk for surgery.[67] These valves consist of pericardial valve substitutes that are mounted on expandable stents. Results of these procedures are encouraging, but significant long-term results are not available for this technology.

### Aortic Insufficiency

The therapy for aortic valve regurgitation is primarily afterload reduction with vasodilating agents to discourage regurgitation and prevent pathologic remodeling of the myocardium.[68]

## INDICATIONS FOR SURGERY

### Aortic Stenosis

All patients with severe aortic valve stenosis and symptoms should be considered for traditional valve replacement. These patients tend to have aortic valve areas of less than 1 $cm^2$ associated with a mean gradient exceeding 40 mm Hg.[68] Asymptomatic patients with AS meeting these criteria should also be considered for valve replacement secondary to the small but real incidence of sudden death associated with the natural history of this lesion. The benefits of early surgical intervention for asymptomatic patients with severe AS are clearly identifiable in a clinical study recently reported by Kang and associates.[69] These investigators identified patients with severe asymptomatic AS and compared the long-term outcomes of those treated with conventional therapy versus those treated with early elective valve replacement. Importantly, the latter group realized a significantly higher estimated actuarial 6-year cardiac mortality compared to those patients treated with conventional therapy.[69] Thus, early surgical intervention for asymptomatic patients with severe AS and relatively low operative risk may be a worthwhile treatment strategy.

### Aortic Insufficiency

Severe AI associated with gradual ventricular dilatation and at least New York Heart Association Class II symptoms of fatigue and congestive heart failure are deemed appropriate indications for surgery. In addition, symptomatic, moderate AI with mild-to-moderate (EF >25 percent) LV dysfunction should be referred for AVR. A symptomatic patients should be considered for surgery if there is LV systolic dysfunction or severe LV dilatation (end-diastolic dimension >75 mm or end-systolic dimension >55 mm).[68,70–73]

## SURGICAL THERAPY

### Positioning, Incisions and Cardiopulmonary Bypass

The patient is placed in the supine position. Monitoring lines such as a radial arterial catheter and pulmonary arterial catheter can be placed in the holding area under sedation or after the patient is brought into the operating room. Despite excellent advances in cardiothoracic anesthesia, the occasional patient with severe AS will suffer cardiac arrest during anesthetic induction. It is therefore advisable, in cases of severe AS, for the surgeon to be immediately available from the time the patient is brought into the operating room. The patient's chest, abdomen, perineum, and lower extremities are prepped and draped in sterile fashion. Median sternotomy is the classic mode of access to the heart, but minimally invasive approaches such as upper hemisternotomy[74] and right parasternotomy[75] have been described. Tacking only the right side of the incised pericardium to the retractor or skin allows the ventricular mass to rotate posteriorly and improve access to the aortic root. The patient is systemically heparinized to reach a blood activated clotting time (ACT) of 480 s. Cardiopulmonary bypass is established using dual-stage or

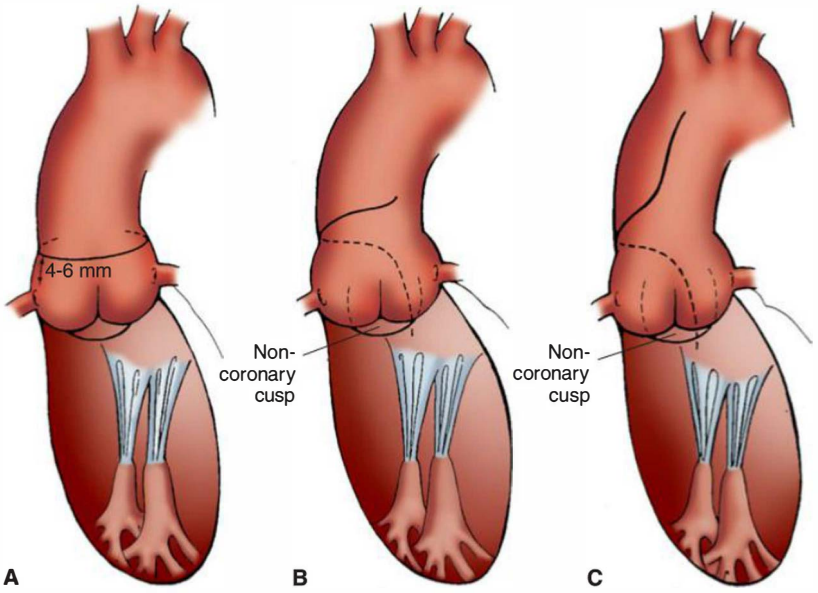



**FIGURE 32-1** Aortotomy incisions. (Reproduced with permission from David TE. Mechanical and bioprosthetic aortic valve replacement. In: Edmunds LH (ed). *Cardiac Surgery in the Adult*. New York: McGraw-Hill, 1997:859–910.)

bicaval cannulation with a LV vent placed across the mitral valve via the right superior pulmonary vein or through a stab incision in the LV apex. Mild-to-moderate systemic cooling (32°C) is used. If the valve is not regurgitant, cold blood cardioplegia should be delivered antegrade via the aortic root for more uniform myocardial distribution, then intermittently via a retrograde coronary sinus catheter for the duration of the cross-clamp period. If the retrograde catheter cannot be inserted blindly, options include bicaval cannulation and insertion of the retrograde coronary sinus catheter across the visualized coronary sinus orifice, or delivery of antegrade cardioplegia via perfusion catheters positioned or sewn into the coronary ostia. Numerous approaches to aortotomy have been described, the most common being the oblique aortotomy and near-transection aortotomy (Fig. 32-1). The oblique aortotomy begins in the anterior midline of the ascending aorta or just along the left anterior side and extends to the right and inferoposterior into the midportion of the noncoronary sinus. The near-transecting aortotomy should be made 1.0 to 1.5 cm above the origin of the right coronary artery for the best visualization. Therefore, added dissection is required on the anterior surface of the aorta to identify the right coronary artery takeoff, which can occasionally result in damage to the right coronary artery necessitating either repair or vein graft bypass of the right coronary artery. The near-transecting aortotomy is relatively easy to close but troublesome bleeding may occur posteriorly, which can be difficult to manage. In addition, if a small aortic root is encountered such that annulus enlargement is necessary, a right-angle incision must be made in the aorta and extended across the annulus, which can be very challenging to close later. Finally, since the sino-tubular junction is 10 to 15 percent smaller in diameter than the annulus, occasionally it will be very difficult to pass an appropriately sized aortic valve across the aortotomy to the annulus, especially if the aorta has lost some of its elastic properties due to calcification. The oblique aortotomy eliminates many of these concerns and is recommended by the authors. The aortic valve is inspected and the locations of the coronary ostia are identified. The valve is then carefully excised, taking care not to button-hole the aorta or damage the aorto-mitral continuity by incising too deeply. Careful debridement of all calcific matter is then undertaken where necessary followed by irrigation with cold saline to remove particulate matter (Fig. 32-2). The choice of valve and techniques of implantation are discussed below. Systemic rewarming is begun at an appropriate point in the implantation procedure so as to not impose extra time waiting for the patient to reach normothermia prior to separation from cardiopulmonary bypass. Following valve implantation, a careful inspection is performed to confirm correct seating of the valve and ensure that both coronary artery ostia are unobstructed. Also, a final check for the absence of residual particulate matter should be undertaken. The aortotomy is closed with running polypropylene suture and a de-airing vent is placed in the most anterior portion of the ascending aorta. The ventricular vent is removed. A warm cardioplegic infusion is given and the cross-clamp is removed with the patient placed in the Tendelenburg position. Ventricular and atrial pacing wires are placed and mechanical ventilation is resumed. De-airing maneuvers such as lung hyperinflation, side-to-side shaking of the chest, and manual agitation of the heart are performed with the heart partially ejecting. Transesophageal echocardiography is very helpful in assessment of de-airing, and also

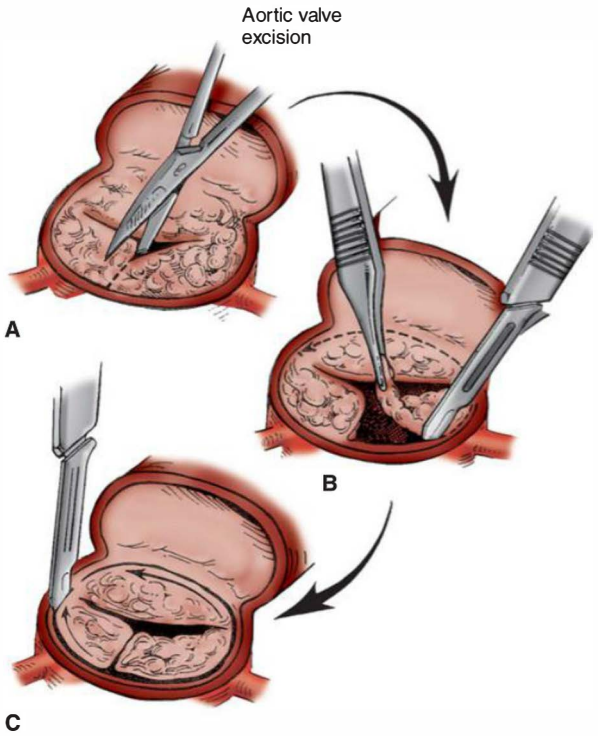



**FIGURE 32-2** Technique of excision of the aortic valve. (Reproduced with permission from David TE. Mechanical and bioprosthetic aortic valve replacement. In: Edmunds LH (ed). *Cardiac Surgery in the Adult*. New York: McGraw-Hill, 1997:859–910.)

in the interrogation of the valve for correct leaflet function and absence of perivalvular leaks. The patient is weaned from bypass at a systemic temperature of 36.5°C with good ventilation parameters. Protamine is given slowly by the surgeon directly into the ascending aorta, and the patient is decannulated. Meticulous hemostasis is obtained, a midline mediastinal drain (36F thoracostomy tube) is placed, and the patient is closed in the standard fashion.

## Which Type of Valve to Use?

Subcoronary homograft aortic valves are technically more difficult to implant than stented and stentless bioprostheses and should be considered for younger patients in centers that have extensive experience with homograft valve replacements.

Prosthetic valves have the advantage of relative ease of implantation. Bioprosthetic valves have no requirement for anticoagulation postoperatively but there are two drawbacks associated with these valves. The first is the introduction of a residual transvalvular gradient (especially with smaller valve sizes), which may impede the rapidity and extent of LV mass regression after valve replacement. The second drawback, the true "Achilles' heel" of tissue bioprostheses, is structural valve deterioration requiring reoperation for valve re-replacement. The latest-generation tissue bioprostheses such as the Carpentier–Edwards bovine pericardial[76–78] and Hancock II[31,79] porcine valves are comparable in results and have 80 to 93 percent freedom from structural valve failure at 10 to 14 years. These failure rates are accelerated in younger patients and in patients with renal failure. This type of valve is clearly most appropriate for older patients (i.e., greater than 70 years of age). However, concomitant cardiac disease (e.g., CAD) lowers the age at which one tissue valve will suffice for the patients' lifetime by 5 to 10 years.[80] Also, concomitant use of oral lipid lowering agents appear to have an important protective effect, with reduction of valve deterioration.[81,82] Having stated the above, the risk of operative mortality with isolated aortic valve reoperation is only 5 to 10 percent,[83–85] making tissue valve replacement a reasonable option even in younger patients not interested in taking oral anticoagulants and also in centers that do not perform a high volume of more complex aortic valve and root procedures.

Mechanical valves leave significant residual transvalvular gradients in smaller sizes as with stented bioprostheses, and all require oral anticoagulation. Use of oral warfarin is associated with a significant incidence of bleeding and thromboembolic complications.[86,87] A recent long-term retrospective review performed by Toole and colleagues reported that freedom from thromboembolism and bleeding at 25 years was 69 ± 5 percent and 67 ± 3 percent, respectively, in patients that underwent AVR with a St. Jude Medical mechanical prosthesis at a single-center institution.[86] Thus, a younger individual requiring AVR must make a choice between accepting the risk of an aortic valve reoperation with bioprosthetic valves versus the risk of bleeding and thromboembolic complications related to long-term oral use of warfarin.

## Valve Implantation Techniques and Results

### STENTED AORTIC VALVE REPLACEMENT

Following excision of the native aortic valve, the annulus is measured using the sizers provided by the company for the valve type selected. Valve sutures are placed in horizontal mattress fashion across the remaining aortic annulus and sequentially placed across the sewing ring of the prosthesis. The prosthetic valve is then carefully seated so as to avoid obstructing the coronary artery ostia, followed by tying and cutting of all of the sutures and closure of the aorta. Certain valves are designed to be implanted in an intraannular position (such as certain St. Jude models), necessitating placement of everting (aorta to ventricle) sutures, and others are designed for supraannular seating (such as the Carpentier–Edwards pericardial prostheses), requiring placement of noneverting (ventricle to aorta) sutures. Pledgetted or nonpledgetted sutures are used; there are no conclusive data supporting superiority of one over the other. In addition, some surgeons implant the prosthesis with a continuous running suture (Fig. 32-3). While it is intuitively obvious that

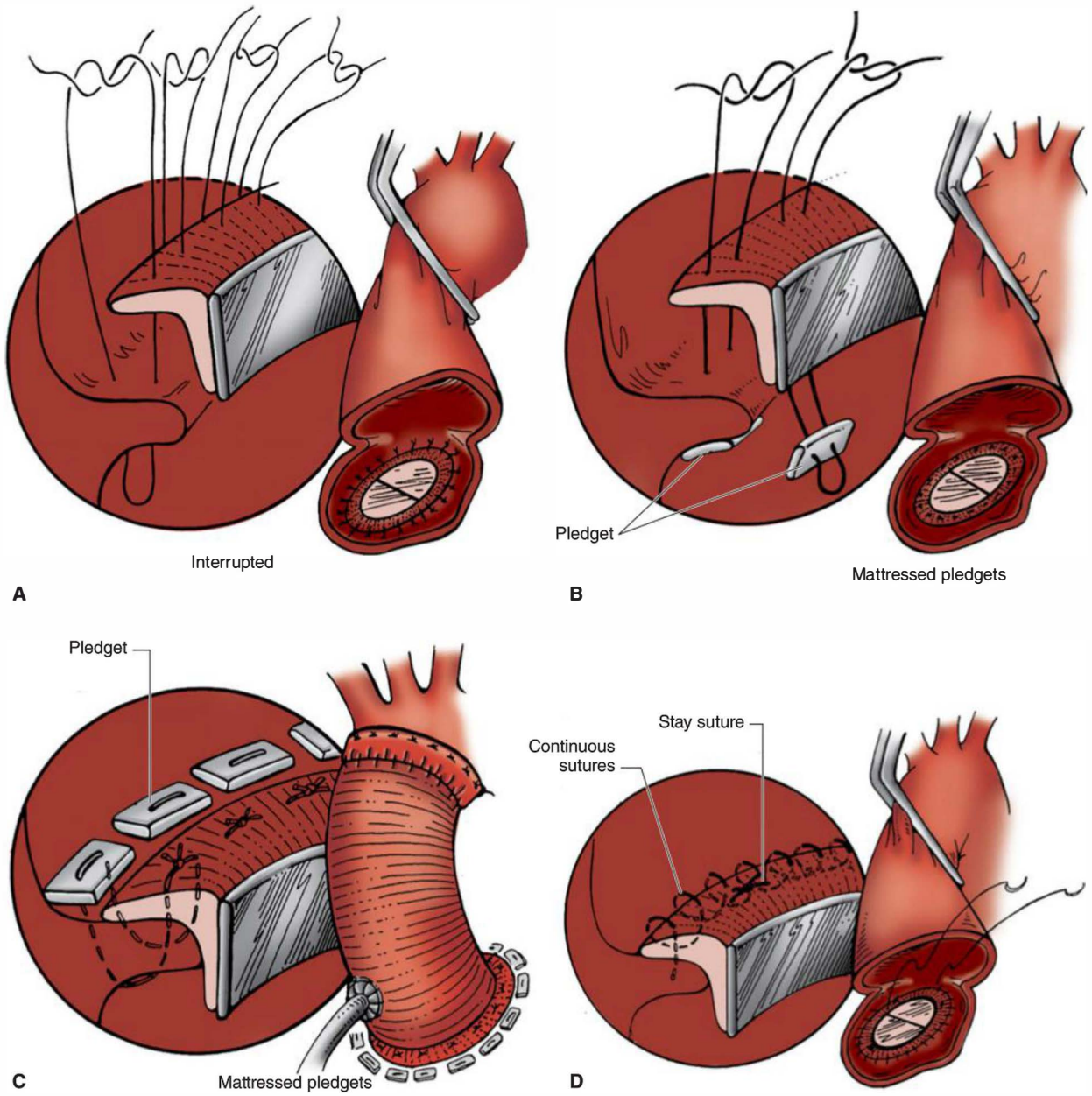



**FIGURE 32-3** Annular suturing techniques. **A.** Interrupted sutures. **B.** Noneverting mattressed pledgets. **C.** Everted mattress pledgets with replacement of ascending aorta and aortic valve. **D.** Continuous running suture. (Reproduced with permission from David TE. Mechanical and bioprosthetic aortic valve replacement. In: Edmunds LH (ed). *Cardiac Surgery in the Adult*. New York: McGraw-Hill, 1997:859–910.)

the largest valve size possible should be implanted, patients with severe LV hypertrophy resulting in intracavitary (i.e., subannular) gradients may actually be reliant on the stenotic native valve to impose sufficient afterload to prevent systolic ventricular collapse before ejection of an adequate stroke volume. In this uncommon situation, it may be appropriate to implant a *smaller* valve to impose a higher residual transvalvular gradient to encourage proper emptying of the ventricle. Alternatively, an interventricular septal myectomy/myotomy may help eliminate the intracavitary gradients in these unusual situations.[88]

The results with stented tissue prostheses continue to improve with each successive iteration. The latest-generation tissue bioprostheses such as the Carpentier–Edwards bovine

pericardial[76–78] and Hancock II[31,79] porcine valves are comparable in results and have 80 to 93 percent freedom from structural valve failure at 10 to 14 years.

Important clinical results pertaining to the use of mechanical valves in the aortic position primarily focus upon risks associated with bleeding and thromboembolic events. The longest data are available for the St. Jude mechanical prosthesis, where actuarial freedom from reoperation, thromboembolism, and bleeding following AVR at 25 years is 90 ± 2 percent, 69 ± 5 percent, and 67 ± 3 percent, respectively.[86]

### THE ST. JUDE STENTLESS VALVE

This valve is usually implanted via a transecting aortotomy approximately 1.0 to 1.5 cm distal to the origin of the right coronary ostium. After the native valve is excised, the sewing ring is attached in planar fashion at the aortic annular level with simple interrupted sutures. Following this (since this valve has no supporting stent), the valve is fixed to the patient's own aorta by sewing the rim of porcine aorta to the patient's aorta. The valve must therefore be carefully seated with the first set of interrupted sutures so that the second suture line does not obstruct the coronary ostia with proper orientation of the valve leaflets. This valve is therefore more challenging to implant than the stented prostheses, but offers the advantage of lower valve gradients, especially with smaller valve sizes.[89] The most recent data show freedom from hemodynamically significant valve insufficiency to be 82.5 percent at 9 years with 90.1 percent freedom from reoperation.[90] Anticoagulation is not required with this valve.

### MEDTRONIC FREE-STYLE PROSTHESIS

The Medtronic free-style prosthesis preserves most of the porcine aortic root and is not reinforced by stented or prosthetic fabric. The Medtronic free-style prosthesis offers the advantage of tailoring to multiple operations, including full aortic root replacement and trimming of the prosthesis for subcoronary valve replacement. The subcoronary operative technique is similar to that for the St. Jude stentless aortic valve except that the free-style aorta is scalloped to allow for both coronary ostia on the left and right sinus but typically not scalloped over the noncoronary sinus. Results of the Medtronic free-style prosthesis used as a full aortic root replacement are available to 8 years.[91] At this time, freedom from AI was 100 percent, and there were no cases of structural valve deterioration observed, with 100 percent freedom from reoperation.[91] Comparison with the St. Jude stentless valve suggests less insufficiency and lower transvalvular gradients with the free-style prosthesis.[92] Anticoagulation is not required with this valve.

### SUBCORONARY HOMOGRAFT AORTIC VALVE REPLACEMENT

For insertion of a homograft, it is generally recommended that a transecting or near-transecting aortotomy be used, though some authors have described the use of a lazy incision starting anteriorly and going to the patient's right, but ending at a level well above the expected top of the allograft commissure. By following resection of the aortic valve, the aortic annulus can be sized with a Hagar dilator or any convenient prosthetic valve sizer. To correct for the thickness of the LVOT muscle the allograft should be 2 to 3 mm smaller than the measured size of the annulus. At this point, the allograft ventricular outflow tract muscle should be trimmed to debulk it, but leave enough support for suturing and attachment of the valve cusps. Approximately 5 to 7 mm of outflow tract should be left below the valve cusps to allow adequate suturing to the annulus. In addition, if there is residual anterior leaflet of the mitral valve, this can be excised in a planar fashion. Some authors recommend that the homograft not be implanted in anatomical fashion, but rather that it be rotated 120° counterclockwise so that the outflow tract muscle does not abut onto the septum of the interventricular septum of the recipient. Following this, stay sutures are usually placed at 120° intervals in the graft corresponding to the nadirs of the commissures for orientation. Suturing of the homograft to the annulus can be performed in continuous fashion with running 4-0 polypropylene suture or interrupted fashion with running 4-0 polyester sutures placed in simple interrupted fashion. This may be facilitated by inversion of the entire homograft into the LVOT of the recipient, thus making visualization for suturing much easier. Following this, the homograft sinuses are trimmed away so as to not obstruct the left and right coronary ostia and the residual homograft aorta around the commissures is sutured to the native aortic wall with a running 4-0 polypropylene suture. The aortic wall in the area of the noncoronary sinus can be left untrimmed to facilitate implantation. Although homograft aortic valve placement can be technically challenging, results with this technique are excellent with freedom from reoperation rates in adults of 81 to 93 percent at 15 years,[93] with no anticoagulation required.

## Postoperative Care and Surgical Results

Immediate postoperative care should focus on control of hypertension (for which intravenous sodium nitroprusside or nicardipine is most commonly used) and maintenance of adequate filling pressures (central venous pressure 10–15 mm Hg, pulmonary capillary wedge pressures in the 15–18 mm Hg range). Dual-chamber pacing is required in a small proportion of patients who leave the operating room in conduction block. Often this resolves within 24 to 48 h. If conduction block persists greater than 4 to 5 days, permanent pacemaker insertion should be considered. In patients with no conduction disturbances, pacemaker wires can be removed on the third or fourth postoperative day. The patient should be placed on telemetry for the duration of the hospital stay, however. The mediastinal tube is removed for outputs less than 150 mL/24 h period.

Patients with mechanical valves are started on oral warfarin on the second postoperative day. Use of daily aspirin

coupled with a target international normalized ratio (INR) of 2.0 to 2.5 provides satisfactory anticoagulation and minimizes long-term bleeding and thrombotic events. Patients with bioprosthetic valves can be managed with aspirin alone, with no warfarin required.

The 30-day (early) mortality for AVR varies from 2 to 5 percent. This number is approximately doubled with redo operations. Preoperative variables independently predictive of early mortality include advanced age, renal insufficiency, New York Heart Association class III or IV status, poor ventricular function, concomitant CAD, and aortic cross-clamp time.

Reoperation for mediastinal hemorrhage should be required in less than 5 percent of cases. Perivalvular leaks occur in 1 to 2 percent. Complete heart block requiring pacemaker insertion occurs in about 1 percent in most series. Stroke occurs in approximately 1 to 2 percent of patients. There is no practical pharmacological strategy for the prevention of postoperative atrial fibrillation, which occurs up to one-third of the time (in patients with no previous history). Careful correction of electrolytes and chemical cardioversion with intravenous and oral amiodarone is preferred and successful 90 to 95 percent of the time. Patients should then be maintained on oral amiodarone for approximately one month by which time the threat of recurrent atrial fibrillation should be resolved. In patients requiring warfarin, use of amiodarone will make it very difficult to manage the INR, and consideration should be given to alternative antiarrhythmics such as procainamide or sotalol. Patients with persistent atrial fibrillation despite attempts at chemical and electrical cardioversion should be maintained on oral warfarin until either the arrhythmia resolves or electrical cardioversion can be performed.

## Patient–Prosthesis Mismatch

Important objectives of AVR are to minimize postoperative gradients and optimize and accelerate the normalization of LV mass regression. Occasionally, the situation arises where the implanted prosthetic valve has a gradient that is sufficiently severe so as to prevent a resolution of the physiology associated with valvular disease resulting in "patient–prosthesis mismatch." Patient–prosthesis mismatch is expressed in terms of the EOA obtained from charts published by each valve company. The EOA is standardized to body surface area (EOAI) and is suggested to be present for EOAI <0.85 to 0.90 $cm^2/m^2$.[94] A number of studies have attempted to investigate whether insertion of a small prosthesis influences short- and long-term survival. Given the fact that early and late survival after AVR is usually related more to concomitant disease processes in the valve itself, it is not surprising that many studies have not found a relationship between early and late survival in aortic valve prosthesis size. A very large study from the Cleveland Clinic by Medallion and Colleagues was unable to detect an adverse impact on survival of moderate patient–prosthesis mismatch.[95] In contrast, a study by Kratz and colleagues suggested that patients with a body surface area of greater than 1.9 $m^2$ who received the St. Jude Valve size 19 or 21 mm had a greater probability of late sudden death.[96] The study by Adams and colleagues found that insertion of a 19-mm stented bioprosthesis or mechanical valve with elderly men with AS was associated with a higher operative mortality and therefore recommended that an annulus enlarging procedure be performed in these patients.[97] However, it is important to remember that performance of an annulus enlarging procedure increases the mortality and morbidity associated with AVR and this should be kept in mind when considering this procedure. More recently, three large studies have helped to clarify the survival effect of patient–prosthesis mismatch on survival. Rao and associates[98] examined a cohort of 2981 patients undergoing AVR; they observed that smaller prosthesis–patient size was associated with greater operative mortality but did not affect overall 12-year survival. Hanayama and colleagues found, in a study of 1129 patients, that prosthesis–patient size did not influence survival, New York Heart functional class, or LV mass index.[99] Finally, Blackstone et al. examined data on 13,258 AVRs from nine data sources to address the question of prosthesis–patient size and mortality after AVR.[100] In this study, 30-day mortality increased 1 percent to 2 percent when indexed orifice area decreased to less than 1.2 $cm^2/m^2$ or standardized orifice size decreased to less than –2.5 Z. However, no expression of prosthesis–patient size was associated with reduced intermediate-term (0.5–5 years) or late-term (5–15 years) survival. In contrast, patient risk factors, such as age, had a profound effect on survival.[100]

Rather than considering the impact of valve prosthesis on survival, efficacy of regression of LV hypertrophy may be a more sensitive indicator of the adequacy of a selected prosthesis. Regression of LV mass after AVR is demonstrated within the first few weeks after surgery and extends out to about 6 months postoperatively.[101,102] The effects of prosthesis size on regression of the LV mass have proven to be somewhat controversial, as some authors have found that insertion of 19 and 21 mm stented and mechanical valves are associated with rates of regression similar to those observed with use of larger prostheses.[103,104] On the other hand, other studies have shown slower regression of LV mass.[105] What is clear is that reverse LV remodeling occurs over a variable time course after AVR for AS.[55] For example, in a seminal clinical investigation, Monrad and colleagues observed significant reductions in LV muscle mass at both intermediate (1.6 ± 0.5 years) and late (8.1 ± 2.9 years) time points as compared to values obtained in the same patients prior to valve replacement.[55] Similarities in LV muscle mass values between AS patients treated with AVR and control subjects was only observed at late time points suggesting that reverse LV remodeling occurs over a period of years. Controversies pertaining to patient–prosthesis mismatch are further confounded by the fact that the labeling of prosthetic valves and valve sizes do not bear a consistent relationship to the internal diameter of the valve orifice, which is probably the most important

hemodynamically significant dimension in terms of postoperative gradients.[106] For example, the internal diameter of a St. Jude standard mechanical valve that is labeled as 21 mm is actually 16.7 mm and the internal diameter of the MO Hancock II Porcine that is labeled as 21 mm is 18 mm. These discrepancies are particularly important in the management of a small aortic root in which insertion of an unnecessarily small prosthesis may result in very high postoperative gradients. In addition, comparison of the hemodynamic characteristics of various valve types become very difficult to judge based on these parameters.

In the light of the above, the impact of patient–prosthesis mismatch of postoperative outcomes following AVR remains somewhat controversial. EOA index may be used to identify those patients having a "small aortic root" in the operating room, hence helping the surgeon plan the appropriate valve replacement strategy. Following calculation of the patient's body surface area, excision of the diseased aortic valve and annular debridement, the aortic annulus is sized using the appropriate sizer for the valve of intended use. The EOA for this valve size is then taken from a chart published by the valve company. If the EOAI is less than 0.85 to 0.90, the aortic annulus may be considered to be small.

## Management of the Small Aortic Root

The fundamental goal of the management of a small aortic root is to avoid insertion of an unnecessarily small prosthesis. In general, the surgical options include use of a small, stented prosthesis, mechanical dilatation of the aortic root, implantation of stentless tissue valves, supraannular positioning of the valve replacement device, implementation of an annulus enlarging procedure, and in certain cases, application of the apicoaortic conduit technique. A useful rule of thumb is to remember that increasing the valve size by two increments in general results in the reduction of cardiac stroke work of approximately 40 percent, roughly equivalent to the insertion of an intraaortic balloon counter-pulsation device.

### USE OF A SMALL STENTED PROSTHESIS

Given the above discussions, it may be appropriate in certain situations to accept implantation of a small prosthesis that by calculation would result in patient–prosthesis mismatch. Examples of such situations would include elderly, inactive patients, patients with multiple other comorbidities in whom a fast, relatively simple operation is mandatory for the best outcome, or an aortic root that is so calcified that other valve replacement options may be technically impossible.

### MECHANICAL DILATATION OF THE AORTIC ROOT

Anecdotal reports have documented successful insertion of larger prosthesis after mechanical dilatation of the aortic root.[107] There are, however, very little data regarding the overall safety of this procedure and the amount of annulus enlargement achievable. Caution must be exercised when considering this option.

### IMPLANTATION OF STENTLESS TISSUE VALVES

When compared to stented bioprostheses, stentless bioprostheses in general have been confirmed to be hemodynamically superior to various valve sizes. Because of the obliteration of the thick stent with stentless tissue valves, it is often possible to implant a larger valve with a larger internal orifice area than if the stentless valve were used, thus resulting in lower postoperative gradients.[108,109] For example, in patients in which a 19-mm Carpentier–Edwards supraannular pericardial valve fits tightly into the annulus, it is usually possible to fit a 21 or 23 mm St. Jude stentless valve. Successful implantation of this valve is also dependent on the aortic root tissue being pliable and not extensively calcified such that suturing to it is possible.

### SUPRAANNULAR POSITIONING OF THE VALVE PROSTHESIS

Because the noncoronary sinus at its nadir may be lower than the nadir of the left and right aortic sinuses, the prosthesis can sometimes be implanted in the supraannular position within the noncoronary sinus.[110] The prosthesis is then sutured along the aortic annulus and the left and right coronary sinuses, but attached by pledgetted mattress sutures with the pledgets outside the aorta in the noncoronary sinus. This technique may allow implantation of a prosthesis that is one size larger than the size of the aortic annulus. Because the prosthesis crosses the aortic annulus, improper debridement of the annulus in this area may result in paravalvular leaks. A residual shelf of annular tissue will still exist under the prosthesis, which may contribute to a subvalvular gradient.

### ANNULUS ENLARGING PROCEDURE

The Nicks[111] procedure allows for implantation of a prosthesis that is approximately two sizes larger than the measured size of the aortic annulus. This involves the extension of the aortotomy into the nadir of the noncoronary sinus and into the basal third of the anterior leaflet of mitral valve. An autologous pericardial patch or Dacron patch is fashioned in tear-drop shape and the wide portion of the tear drop, up to 4 cm in transverse diameter is positioned downward into the mitral valve. Valve sutures or polypropylene sutures are then used to suture the patch along to the anterior leaflet of the mitral valve across the annulus and up the ascending aorta. Valve implantation sutures are placed across the patch itself in addition to the remainder of the annulus and the remainder of the aortotomy is closed incorporating the Dacron patch (Fig. 32-4).

A second type of annulus enlarging procedure known as the Manouguian[112] procedure involves extension of the aortotomy more posteriorly to the commissure of the non- and

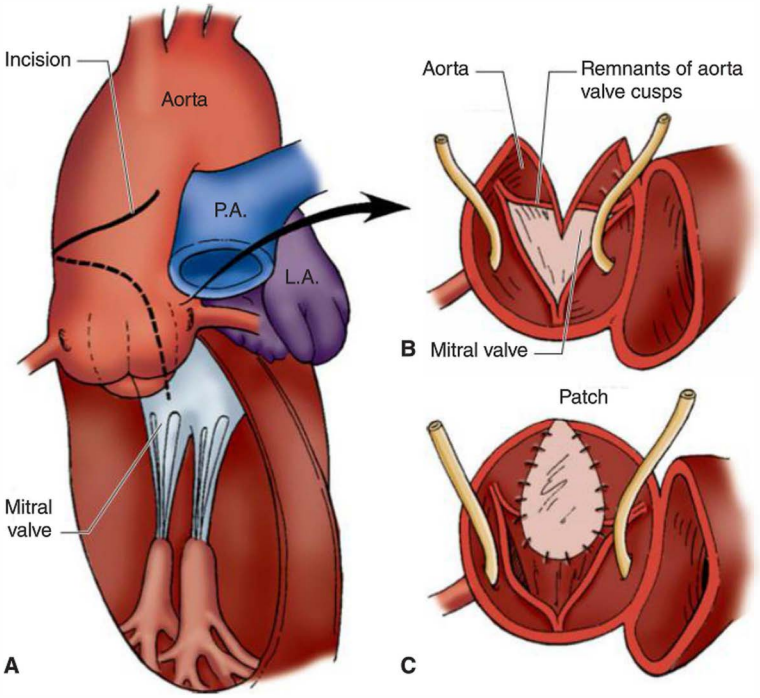



**FIGURE 32-4** Patch enlargement of the aortic annulus at the noncoronary sinus (Nicks procedure). **A.** The aortotomy incision continues downward toward the middle noncoronary sinus. **B.** The incision crosses the aortic annulus into the mid-mitral portion of the anterior mitral leaflet to the roof of the right atrium. **C.** The incision has extended into the upper third of the mitral leaflet. The width of the patch should not exceed twice the length of the incision into the anterior mitral leaflet. (Reproduced with permission from David TE. Complex operations of the aortic root. In: Edmunds LH (ed). *Cardiac Surgery in the Adult*. New York: McGraw-Hill, 1997:939–957.)

left coronary cusps. The incision is then carried through the aortic–mitral septum and onto the anterior leaflet of the mitral valve for up to 2 cm, which also opens the roof of the left atrium. A pericardial patch is then sutured along the mitral valve incision and the aortotomy as with the Nicks procedure. The prosthesis is then secured to the patch with horizontal mattress sutures that may be first placed through the opened roof of the left atrium, thus closing the atriotomy in the process. Alternatively, the atriotomy can be sutured to the patch with a second suture line. The remainder of the aortotomy may then be closed.

A third more radical approach to the small aortic root is known as the Konno–Rastan procedure or aortoventriculoplasty.[113] Its use in the small aortic root associated with aortic valve disease is becoming rare and is, in general, reserved only for enlargements in patients with congenital AS who present later in life for AVR or with other forms of complex congenital heart disease. Here the enlarging incision is made to the left side of the right coronary artery and into the ventricular septum and free wall of the right ventricle. Next, a patch is used to repair the intraventricular septum and a second patch is used to close closure of the right ventricular free wall defect as well as completing the annular enlargement.

As stated previously, it is important to remember that the operative risk with AVR may be increased with an annulus enlarging procedure, with one series quoting 3.5 percent operative risk without annulus enlargement compared to 7.1 percent with annulus enlargement.[114]

### VENTRICULAR APICOAORTIC CONDUIT

Finally, in patients in whom it is not possible to deal with an excessively small aortic root, such as with fibrous tunnel formation, tubular hypoplasia of the ascending aorta, and recurrent aortic valve stenosis unrelieved by aortic root repair or a valvotomy, ventricular apical aorta conduits have been used as a procedure of last resort.[115,116] The patient is approached by a left lateral thoracotomy based on the fifth intercostal space. A valved conduit is then sutured in end-to-side fashion to the descending thoracic aorta. Following this, cardiopulmonary bypass is established and a second graft is sutured to the apex of the left ventricle with the aid of induced fibrillation. The two conduits are then trimmed to length and sutured together, completing the operation (Fig. 32-5). The transthoracic approach gives direct access to the descending aorta and avoids a redo sternotomy. The technique, which is relatively simple to perform, does not compromise major coronary arteries, the conduction system, or other valves; and may be useful in patients who are not good candidates for other, more conventional procedures.

## Aortic Valve Replacement with Concomitant Coronary Artery Disease

Many patients with aortic valvular disease have concomitant CAD, but the data are limited regarding optimal strategies

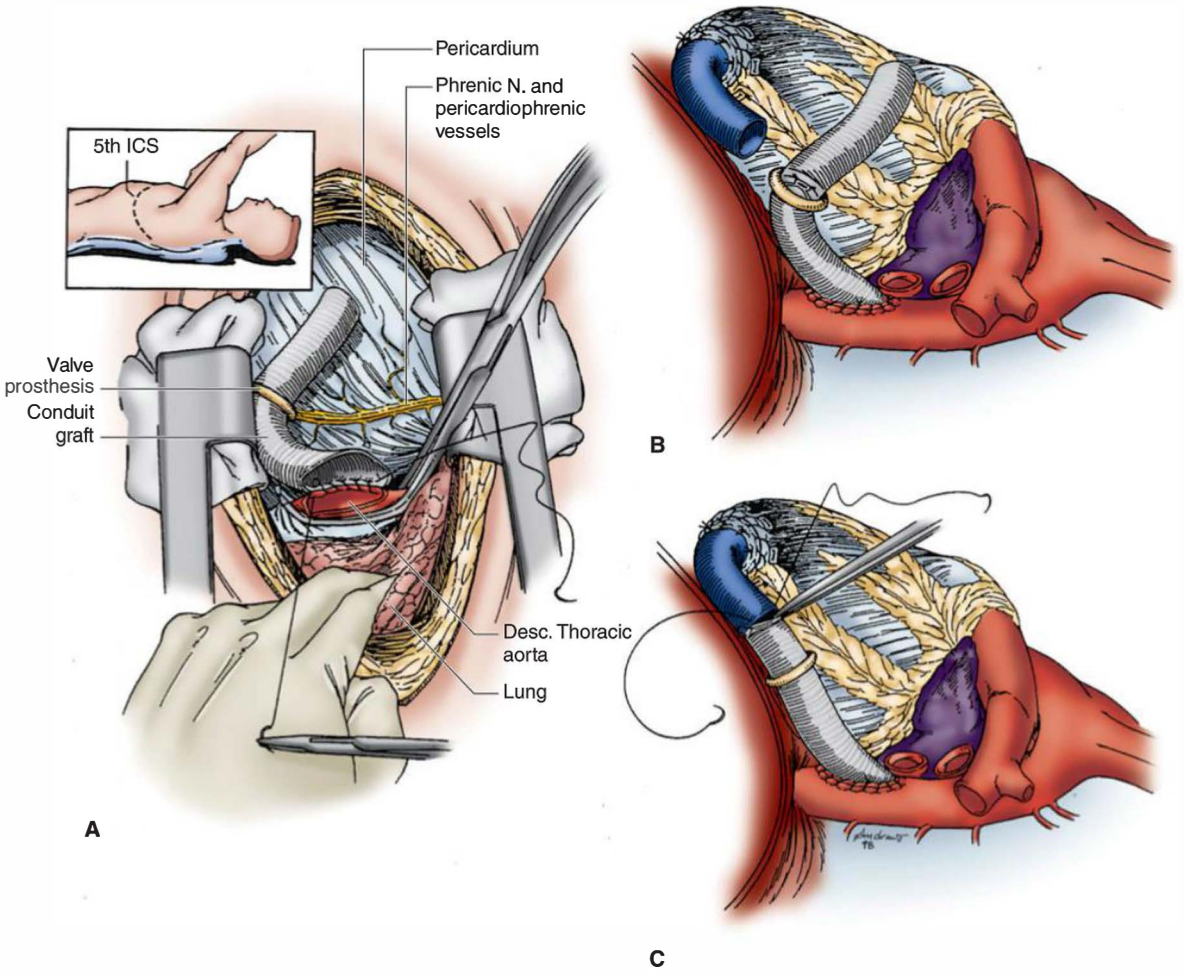



**FIGURE 32-5** Placement of apicoaortic conduit. **A.** After positioning patient in the right lateral decubitus position, the left hemithorax in entered through the fifth intercostal space. The descending thoracic aorta is partially occluded, and the valved conduit is anastomosed with a continuous 3-0 or 4-0 polypropylene suture. **B.** Under cardiopulmonary bypass, the rigid prosthesis is attached to the apex of the left ventricular via interrupted, pledgeted mattress and continuous sutures. Ventricular fibrillation is induced to facilitate the ventricular attachment. Temporary occluding clamps are used on the grafts during completion of the anastomoses. **C.** The prostheses are then connected with a continuous suture. (Reproduced with permission from Cooley DA, Lopez RM, Absi TS. Apicoaortic conduit for left ventricular outflow tract obstruction: Revisited. *Ann Thorac Surg* 2000;69:1511–1514.)

for diagnosis and treatment of CAD in such patients. Ischemic symptoms in patients with aortic valvular disease may have multiple causes, such as LV chamber enlargement, increased wall stress or wall thickening with subendocardial ischemia, and right ventricular hypertrophy. Because angina is a poor marker of CAD in these patients, coronary arteriography is recommended in symptomatic patients before AVR, especially in men older than 35 years of age, premenopausal women older than 35 years of age with coronary risk factors, and postmenopausal women.[68]

Greater than one-third of patients with AS undergoing AVR surgery have concomitant CAD. Population studies have shown that more than 50 percent of patients >70 years old have CAD. Combined coronary artery bypass surgery at the time of aortic surgery or AVR has had little or no adverse effect on operative mortality. In addition, coronary bypass grafting at the time of AVR reduces the rates of perioperative myocardial infarction, operative mortality, and late mortality and morbidity, compared with patients with significant CAD who do not undergo revascularization at the time of AVR. Incomplete revascularization is associated with greater postoperative systolic dysfunction and reduced survival rates after surgery compared with patients who receive complete revascularization.[117,118] Over the past decade, improved anesthesia and myocardial preservation techniques have been associated with reduced overall operative mortality,[119] and

it has become standard practice to surgically bypass all significant coronary artery stenoses when possible in patients undergoing aortic valve surgery.

It is well agreed upon that all patients undergoing coronary artery bypass surgery who have severe AS, symptomatic or not, should undergo AVR at the time of revascularization.[68] Decision-making is more difficult in patients with mild-to-moderate AS who have CAD requiring coronary bypass surgery. Controversy persists regarding the indications for so-called "prophylactic" valve replacements at the time of coronary bypass surgery in such patients.

It is difficult to predict whether a given patient with CAD and mild AS is likely to develop clinically significant AS after revascularization. The natural history of mild AS is variable, with some patients manifesting a rapid progression of their disease, with a decrease in valve area of up to 0.3 $cm^2$/year and an increase in pressure gradient of 15 to 19 mm Hg/year.[120] The average rate of reduction of valve area is 0.12 $cm^2$/year,[121] but the rate of change in an individual patient is difficult to foresee. Phillips et al. reviewed 100 patients who underwent AVR after previous coronary artery bypass grafting (CABG) where the mean valve gradient was <25 mm Hg at the time of initial operation. The mean time interval to reoperation was 9.0 years (range 1.4–21 years) and the overall operative mortality was 7.0 percent. The authors concluded that given the relatively long time interval between the two operations and the significant decline in reoperative mortality rate in recent years, an expectant approach to concomitant AVR–CABG is warranted.[122] Karagounis and associates reviewed 200 patients requiring CABG who all had AS with peak gradients less than or equal to 40 mm Hg. Of these, 46 underwent combined AVR–CABG at first operation. Over a median follow-up period of 4.2 years, none of the patients who had CABG only at first operation required reoperation for AVR. From these data, the authors recommended CABG only for patients with mild AS.[123] In contrast, Ahmed and colleagues followed 40 patients with mild-to-moderate AS who underwent CABG without AVR. Eleven patients (27 percent) in this study group required reoperation for AVR.[124] Similarly, Hochrein and associates noted a 24.3 percent AVR reoperation rate over a 6-year period in patients receiving CABG alone versus 3 percent in patients who underwent AVR–CABG at initial operation.[125] The results of these two studies suggest that AVR is a reasonable option at the time of initial CABG in this patient population.

Smith et al. performed a decision analysis based on the Society of Thoracic Surgeons national database and have submitted the following recommendations. For patients under 70 years old, AVR for mild AS is recommended if the peak valve gradient is 25 to 30 mm Hg. For older patients, the threshold gradient increases by 1 to 2 mm Hg/year of age. Also, CABG only is favored in patients with slow (<3 mm Hg/year) progression of AS, in contrast to those with rapid progression (>10 mm Hg/year), who should have combined AVR–CABG, with the possible exception of patients >80 years old who have valve gradients <25 mm Hg at the time of surgery.[126] The choice of prosthesis does not influence overall survival, but a bioprosthetic valve is likely more appropriate in this setting because of increased complications related to the requirement for anticoagulation with mechanical valves,[126] and because the decreased patient longevity in patients with significant CAD undergoing AVR with makes structural valve deterioration much less likely.[80]

## Aortic Valve Replacement in End-Stage Renal Disease

AS is common in patients undergoing maintenance dialysis. Abnormalities include annular and valvular thickening, and calcification of one or more of the heart valves, thereby leading to stenosis with or without concomitant regurgitation.

Many predisposing factors are associated with valvular disease in dialysis patients, the most noteworthy being secondary hyperparathyroidism.[127,128] Valvular calcification is associated with an elevated calcium–phosphorus product, hypercalcemia, vascular calcification, and elevated phosphate levels, all findings that can occur in patients with marked secondary hyperparathyroidism. Valvular calcification may also be found in the absence of secondary hyperparathyroidism, particularly among those with bone disease, older patients, and those who have undergone dialysis for a longer duration. The association with a dynamic bone disease may be related to the increasing utilization of calcium-containing phosphate binders and the subsequent development of hypercalcemia.[129] Additional factors that may enhance the development of valvular heart disease in this patient population include the presence of one or more of the following conditions: hypertension, hyperlipidemia, LV hypertrophy, hypertrophic cardiomyopathy, mitral valve prolapse, high cardiac output states, anemia, or infective endocarditis.

The use of bioprosthetic valves in hemodialysis patients was classified as a class III indication by the 1998 American College of Cardiology/American Heart Association Task Force on Practice Guidelines, with valve replacement with a mechanical prostheses is classified as a class II or IIa indication.[68] This recommendation is based on a widely held opinion that the risk of accelerated bioprosthetic valve failure mandates the use of mechanical prosthetic valves in hemodialysis patients.

In a study of over 95,000 patients, Byrne and colleagues reported the survival of all Medicare patients with end-stage renal failure in the United States from 1982 to 1987.[130] The average survival of a patient between 55 and 65 years old, from the time dialysis was started, was 52 percent at 3 years and 33 percent at 5 years. This suggests that the life expectancy among these patients is so poor that there is little need for a prosthetic valve that will endure more than a few years in this population.

Lucke and coworkers[131] reviewed their experience with 19 patients on long-term dialysis undergoing valve replacement from 1979 to 1994. Nine patients received bioprosthetic

valves and 10 received mechanical valves. At a mean follow-up of 32 months, no patient required reoperation for bioprosthesis degeneration; however, patients receiving mechanical valves had a higher incidence of thromboembolism and bleeding, leading the authors to conclude that bioprosthetic valve replacement was the preferable choice. Kaplon et al. reviewed 42 patients on chronic preoperative dialysis underwent valve replacement, of which 17 received mechanical valves and 25 received bioprostheses. Survival at 3 and 5 years was 50 and 33 percent after mechanical valve replacement, and 36 and 27 percent after bioprosthetic valve replacement ($p = 0.3$). Four patients with bioprostheses required reoperation: three for allograft endocarditis and one at 10 months for bioprosthesis degeneration. One patient who received a mechanical valve required reoperation. The authors concluded that since the life expectancy of patients on dialysis is limited, bioprosthesis degeneration will be uncommon and therefore, surgeons should not hesitate to implant bioprosthetic valves in these patients.[132] More recently, Brinkman and associates[133] reviewed 72 patients on chronic dialysis undergoing valve replacement. In the 46 patients with reliable long-term (greater than 30 days) follow-up data, significant bleeding or stroke was documented in 17 of 34 patients with a mechanical valve and 1 of 12 patients with a bioprosthetic valve. The type of valve implanted did not influence early and late survival. The authors concluded that the six-fold higher incidence of late bleeding or stroke in patients on dialysis with a mechanical valve requiring warfarin suggested that bioprosthetic valves are the valve substitute of choice in patients on chronic dialysis. Finally, Herzog and colleagues[134] studied dialysis patients hospitalized for heart valve replacement surgery from 1978 to 1998 from the US Renal Data System database. The in-hospital mortality of 5858 dialysis patients (of which 3415 underwent AVR) undergoing valve surgery was 20.7 percent. There was no significant difference in survival related to type of prosthetic valve. The authors concluded that there was no significant difference in survival of dialysis patients after cardiac valve replacement with tissue versus nontissue prosthetic valves.

The above data indicate that valvular replacement in patients undergoing hemodiaylsis has a poor prognosis, and while either prosthesis choice is a viable option, the weight of evidence tends to support use of bioprosthetic valves in these patients.

## Aortic Valve Replacement in Infective Endocarditis

Infective endocarditis is a highly lethal disease in which a microorganism colonizes a site in the heart and produces a variety of manifestations including fever, sepsis, splenomegaly, and embolic events. With aortic valve endocarditis cardiac abnormalities such as congenitally bicuspid, degenerative and rheumatic valve disease create endocardial "jet lesions," which promote seeding by microorganisms. Common microorganism sources include dental extractions, endoscopy, urinary tract infections, chronic intravenous drug, and requirements for long-term, frequently intravenous access with chronic chemotherapy, parenteral nutrition, or hemodialysis.

Greater than 80 percent of native endocarditis cases are due to streptococci (50 percent) and staphylococci (20 percent). The first line of treatment for subacute endocarditis (usually caused by less virulent strains such as *Streptococcus viridans*) is antimicrobial therapy in endocarditis is guided by identification of the infective organism. The much more fulminant cases of acute endocarditis (often caused by *Staphylococcus aureus*) do not respond well to antibiotics and early surgery is almost always recommended if feasible. PVE also has subacute and acute forms and a wide spectrum of organisms can be responsible. In "early" PVE, endocarditis within the first 2 months after surgery, *Staphylococcus epidermidis* is the most frequent organism. Late-onset PVE more closely follows the profile of native valve endocarditis. *Enterococcus faecalis* and *Enterococcus faecium* account for 90 percent of enterococcal endocarditis, usually associated with malignancy or manipulation of the genitourinary or gastrointestinal tracts. Recently, the HACEK group (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella* species) have become important causes of endocarditis. In addition to bacteria, fungi, especially *Candida,* are important causes of endocarditis in patients with prosthetic valves, compromised immune systems, or IV drug abuse.

Indications for surgical intervention in endocarditis include new-onset, unmanageable congestive heart failure or cardiogenic shock secondary to treatable valvular heart disease, with or without an established diagnosis of endocarditis. Prompt intervention should not be delayed in acute infective endocarditis when symptoms of congestive heart failure initiate. Surgery is indicated in patients with life-threatening hemodynamic instability due to surgically treatable valvular heart disease only if the patient's prospects for recovery are reasonable, with satisfactory quality of life after the operation. Surgery is not indicated if complications (such as severe embolic cerebral damage) or comorbid conditions make the prospect of recovery dismal. Additional indications for surgical intervention in the hemodynamically stable patient with documented infective endocarditis include prolonged failure of antimicrobial therapy demonstrated by cultures persistently positive for bacteria, patients with annular or aortic abscesses, pericarditis, fungal and gram-negative endocarditis (antimicrobial therapy is not efficacious), new-onset heart block, evidence of systemic embolism, and vegetation size. Patients with a vegetation diameter >10 mm have a significantly higher incidence of embolization than those with a vegetation diameter <10 mm.[135]

Aortic valve endocarditis is associated with the highest rate of complications, and surgical intervention is most often indicated. Treatment consists of excision of the infected valve, adequate debridement of perivalvular abscesses, and valve replacement. If the endocarditis appears to be confined to the valve leaflets only, prosthetic valve replacement may suffice. In this setting, there are no data supporting superiority

of either bioprosthetic or mechanical valves. Should the disease extend into the annulus with or without abscess formation, then full debridement followed by tissue allograft is required to reduce postoperative reinfection.[136] Involvement of the aortic–mitral continuity may mandate excision of this area and reconstruction with bovine pericardium in addition to valve replacement (Fig. 32-6).[137] If possible, it is recommended that the patient have at least 2 days of broad spectrum intravenous antibiotics to clear microorganisms from the bloodstream.

Operative mortality for infection limited to only the aortic valve leaflets themselves compares to the operative mortality of isolated uninfected AVR; however, mortality is higher in those with aortic root abscesses or PVE.[137] Published results show an operative mortality for native valve endocarditis of less than 10 percent, and for PVE of between 20 and 25 percent.[138,139] David et al. reported on 62 patients undergoing valvular intervention for active endocarditis, and reported an operative mortality rate of zero for native valve endocarditis and 12.5 percent for PVE.[140] Valve replacement in hemodynamically stable patients results in a favorable outcome in over 80 percent of patients; however, a reinfection rate of 1 to 13 percent can be expected.

PVE, as previously discussed, usually involves a clinical course that initiates with antibiotic therapy and ends with valvular replacement. Patients with documented PVE, treated with antibiotic therapy alone, generally experience very poor outcomes. Survival rates without surgery are in the 20 to 30 percent range.[138] Long-term survival of PVE following valve replacement is approximately 60 percent at 10 years,[141] with a significant risk of recurrent endocarditis. Recent use of aortic root homografts as the first option for replacement

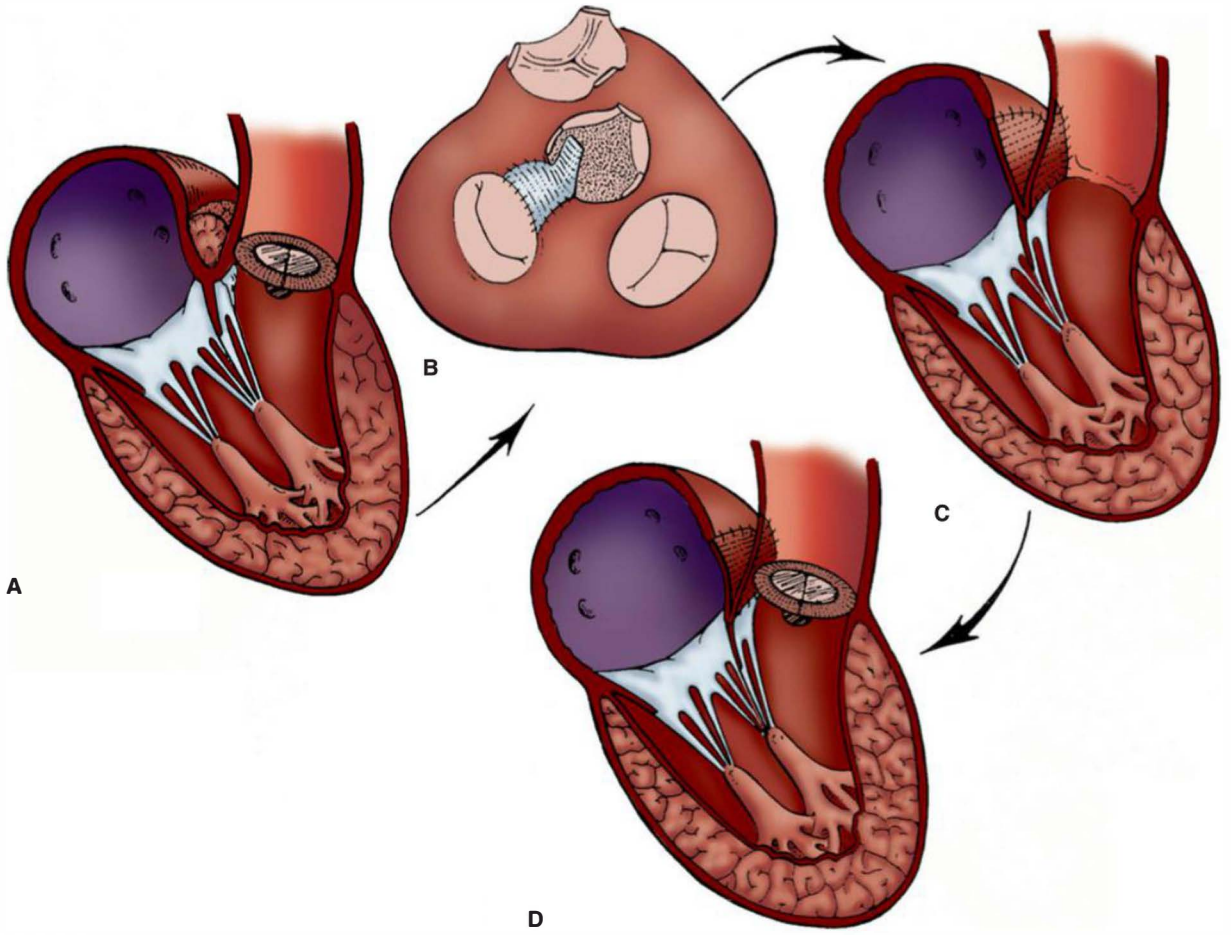



**FIGURE 32-6** Excision of endocardial abscess within fibrous trigone with pericardial patch reconstruction. **A.** Diagram of periprosthetic valvular abscess extending into the fibrous trigone and roof of the left atrium. **B.** Cross-sectional view of the base of the heart with pericardial patch sutured to the fibrous trigone along the mitral annulus, roof of the left atrium, and the aortic root. **C.** Sagittal view of patch reconstructing the aorto-mitral continuity, roof of the left atrium, and the aortic root. **D.** New prosthetic implant inserted. (Reproduced with permission from David TE. Complex operations of the aortic root. In Edmunds LH (ed). *Cardiac Surgery in the Adult*. New York: McGraw-Hill, 1997:939–957.)

have produced improved both early and late survival, and this has become the preferred choice of valve for PVE.[142]

## Aortic Valve Replacement Following Mediastinal Radiation

Mediastinal radiation has been used to treat numerous types of thoracic malignancies over the years including, but not limited to, Hodgkin and non-Hodgkin lymphomas, thymomas, and breast and lung cancers.[143–147] While radiation therapy has proven to be successful in the management of these malignant processes, particularly Hodgkin lymphoma, it is known to lead to cardiac disease, often times many years, if not decades, following radiation exposure.[145,147] The spectrum of radiation-induced mediastinal disease includes acute and constrictive pericarditis, myocardial fibrosis, proximal CAD, conduction abnormalities, and valvular dysfunction.[143–146] Subsequent valvular dysfunction can be particularly problematic as both left-sided valves as well as the fibrous skeleton of the heart may be involved.[143,144] Importantly, the boundaries of radiation exposure and administered dose of radiation appear to correlate with the incidence and severity of subsequent cardiac valve pathology.[143,147] In their retrospective review conducted at the Cleveland Clinic, Chang and colleagues concluded that patients receiving extensive radiation therapy, such as those with Hodgkin lymphoma, had worse short- and long-term survival after cardiac surgical procedures compared to patients who received fewer fractions of radiation therapy for other malignant diseases (i.e., breast cancer) and particularly when delivered in a tangential fashion as opposed to more central delivery.[143] With respect to the aortic valve, both stenosis and regurgitation may be observed following administration of mediastinal radiation and a high index of suspicion for these pathologic cardiac processes should be maintained for those individuals who receive greater than 3500 cGy.[144] Heidenreich and associates echoed this cautionary advice and advocated routine echocardiographic interrogation for all asymptomatic patients subjected to 3500 cGy or more mediastinal radiation. Importantly, in their retrospective review these same authors noted that the incidence of radiation-induced valve pathology increases over time and in a manner that is independent of patient age.[145] Moreover, they reported that the degenerative process occurs for a period of at least two decades following the initial exposure. In other words, a seemingly normal aortic or mitral valve by echocardiographic criteria early after radiation exposure failed to predict a low risk for future valvular pathology.[145] Hull et al. similarly reported that clinically significant valve dysfunction occurred at a median of 22 years following administration of radiation therapy (range, 6–31 years) with a median dose of approximately 3700 cGy (range, 2200–4400 cGy) in patients treated for Hodgkin's lymphoma. It is fortunate that recent refinements in the therapy used to treat patients with Hodgkin's lymphoma, namely, application of combination chemotherapy/radiation regimens, have reduced radiation dose requirements necessary to achieve successful outcomes.[145] Nevertheless, it is likely that cardiac valve pathology will remain a clinical challenge for both patients and cardiac surgeons alike for the foreseeable future. Accordingly, if AVR is to be performed in patients secondary to radiation-induced disease, the proximal coronary arteries should be assessed for flow-limiting stenoses and bypassed as appropriate. In addition, the operating surgeon should be cognizant of the potential for associated proximal ascending aortic calcification and the potential for difficult aortotomy creation and subsequent closure. Because pericardial disease is the most common manifestation of mediastinal radiation, some authors have advocated routine anterior pericardiectomy at the time of valve substitution so as to avoid future complications.[144] However, routine concomitant pericardiectomy remains controversial and has been selectively performed in some centers.[143] Care should be taken in opening the sternum as the innominate vein may be contracted secondary to mediastinal radiation. Aggressive sternal separation with self-retaining retractors may result in an innominate vein tear or avulsion and profuse bleeding.

## Percutaneous Aortic Valve Replacement

Familiarity with endovascular techniques and the recent development of catheter-based valve substitution products has extended relief to patients with severe symptomatic AS who are deemed poor candidates for traditional AVR.[148–151] The balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA) and the self-expanding CoreValve (Medtronic, Minneapolis, MN) (Fig. 32-7) are two transcatheter aortic valve devices that have been approved for use in Europe and are deployed via transfemoral/transapical and transfemoral approaches, respectively. Evaluation of high-risk patients treated with catheter-based transapical AVR in the TRAVERCE (Trans-Apical surgical Delivery of the Cribier–Edwards Aortic Bioprosthesis Clinical Feasibility) investigation revealed a high degree of procedural success (90 percent) as evidenced by correct valve placement, greater than doubling of the aortic valve area, and marked reduction in aortic valve mean gradients.[152] Results from studies evaluating the efficacy of retrograde transfemoral valve insertion are favorable as well and multicenter registries from the United States (REVIVAL II [tRans-catheter EndoVascular Implantation of VALves II] trial) and European Union (REVIVE II [Registry of EndoVascular Implantation of Valves in Europe II]) continue to assess the effectiveness transcatheter AVR via the transfemoral approach in high-risk patients.[148,150,151] A recent prospective study performed by Gotzmann and colleagues assessed hemodynamic results and changes in ventricular function following deployment of the CoreValve via a transfemoral approach.[148] Patient–prosthesis mismatch (indexed aortic valve area $\leq 0.85$ cm$^2$) was observed in approximately 10 percent of the treated patients, a postoperative result not unlike that, and perhaps even more desirable than that observed in patient series treated



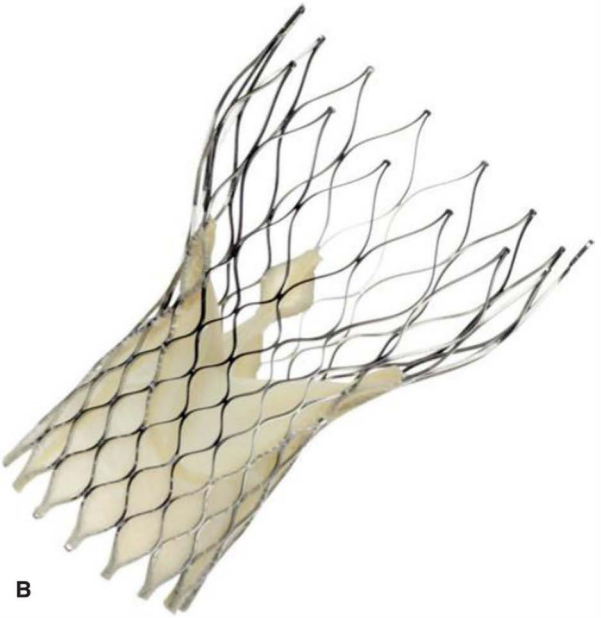




**FIGURE 32-7 A.** Balloon-expandable Edwards SAPIEN valve. (Reproduced with permission from Edwards Lifesciences, Irvine, CA.) **B.** Self-expanding CoreValve. (Reproduced with permission from Medtronic, Minneapolis, MN.)

with conventional AVR.[153,154] Significant decreases in LV mass index were observed 30 days following valve deployment when compared to baseline values and further reductions were noted at 6 months. Significant and substantial reductions in aortic valve peak velocities and mean gradients were noted in the treated patients and their functional status improved markedly. Of importance, a high incidence of paravalvular regurgitation post-valve-deployment appeared to have no untoward effects on ventricular function and dimensions or on overall patient outcomes.[148]

The success of transcatheter AVR hinges upon appropriate patient selection and preoperative evaluation. Inclusion criteria as described by the European Association of Cardio-Thoracic Surgery and European Society of Cardiology include patients with a logistic EuroSCORE or STS score ≥20 or 10 percent, respectively.[155] Clinical considerations for inclusion also include patients with prior mediastinal radiation, prior surgical coronary artery revascularization with patent grafts, marked ascending aortic calcification, severe lung disease, and cirrhosis.[155] Exclusion criteria include patient characteristics pertaining to both vascular and aortic valve anatomy. For instance, transcatheter AVR should be avoided in patients with severely calcified, tortuous, or small iliac arteries and in those patients with severe aortic

angulation, abdominal aortic aneurysms with protruding mural thrombus, or a heavy burden of arch or ascending aortic atheromas. Aortic root and aortic valve annular dimensions require close scrutiny and measurement. Patients with measured annuli <18 mm or >25 mm should not undergo placement of currently available balloon-expandable valves whereas self-expanding prosthesis can be deployed in patients with annuli ≥20 mm and ≤27 mm. Other exclusion criteria include patients with bicuspid aortic valves and those with asymmetric valve calcification as valve deployment may result in incomplete expansion or coronary artery obstruction, respectively.[155] Preoperative assessment should left-heart catheterization, echocardiography, and contrasted computed tomography scans of the entire aorta and vascular circulation to the level of the femoral vessels. These procedures are typically carried out in "hybrid" suites that provide both state-of-the-art fluoroscopic imaging capabilities as well as a setting in which more complicated surgical procedures can be expeditiously carried out in the event that vascular access complications or clinical deterioration is encountered. Potential complications associated with transcatheter AVR include but are not limited to vascular access site injuries (perforation, dissection), coronary artery obstruction, LV apical disruption, significant paravalvular insufficiency, and stroke.[155] Fortunately, this latter complication appears to occur with a frequency of less than 1 percent in a recent investigation.[149]

Irrespective of the transcatheter valve devices selected or the manner in which they are deployed, it appears that this emerging technology is relatively safe and effective in appropriately selected patients. Thus, it appears likely that this technology will be able to be applied to similar patient populations in the United States in the near future, although initial short-term data from the United States PARTNER (Placement of Aortic Transcatheter Valve) trial assessing the effectiveness and safety of the Edwards SAPIEN valve remain to be reported.

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## AORTIC VALVE REPLACEMENT BOARD REVIEW QUESTIONS (CHAPTER 32)

1. Which of the following is true regarding embryology and anatomy of the aortic valve?
   A. The free margin of the left coronary cusp is 1.5 times longer than the hinge point.
   B. The aortic valve forms during the 12th week of embryonic development.
   C. Portions of the noncoronary and left coronary cusps are in continuity with the anterior leaflet of the mitral valve.
   D. The annulus is most robust in the region corresponding to the right coronary sinus, located between the two fibrous trigones.
   E. The three valve layers are relatively devoid of elastin, collagen, and glycosaminoglycans.

2. Which of the following is true regarding aortic valve stenosis?
   A. The left ventricular response typically includes profound eccentric myocyte hypertrophy, progressive myocardial fibrosis, and an increase in chamber compliance.
   B. As LV-wall thickness increases, coronary blood flow is impaired during late systole and flow reserve is reduced.
   C. Severe concentric and septal hypertrophy may not be correctable with valve replacement.
   D. Valve replacement results in complete and rapid (less than 1 month) normalization of systolic and diastolic ventricular function.
   E. Bicuspid valve occurs in 15 percent of the population.

3. Which is true regarding aortic insufficiency?
   A. Isolated insufficiency is usually due to structural abnormalities of the valve causing leaflet elongation and prolapse.
   B. Most patients with acute severe insufficiency can be managed with delayed elective operation.
   C. The enlarging ventricular chamber increases wall stress and ventricular hypertrophy, resulting in an increased diameter to wall-thickness ratio.
   D. Chronic insufficiency causes eccentric fibrosis, which decreases regional stiffness and enhances diastolic relaxation.
   E. Chronic insufficiency is associated with a narrowed pulse pressure and preserved diastolic coronary perfusion.

4. Which is true regarding clinical presentation of aortic valve disease?
   A. Severe stenosis secondary to bicuspid valve usually presents during the seventh decade of life.
   B. Syncope is the most common initial presenting symptom in severe stenosis.
   C. Patients with severe stenosis and angina have a worse prognosis compared to patients with severe stenosis and congestive heart failure.
   D. Patients with severe insufficiency are prone to sudden cardiac death.
   E. Aortic insufficiency has an insidious onset characterized by the gradual development of congestive heart failure and fatigue.

5. Which is true regarding aortic valve replacement?
   A. Enlargement of the posterior annulus is effective therapy for patient–prosthesis mismatch.
   B. Full aortic root replacement with a Medtronic free-style bioprosthesis has been shown to have nearly 100 percent freedom from aortic insufficiency and reoperation at 8 years.
   C. Placement of everting annular sutures generally enables placement of the largest possible prosthesis.
   D. Postoperative patient–prosthesis mismatch is associated with statistically significant reductions in short- and long-term survival.
   E. Homograft aortic valve replacement is associated with early rapid calcification and structural deterioration.

## ANSWERS

1. **Answer: C.** Portions of the noncoronary and left coronary cusps are in continuity with the anterior leaflet of the mitral valve, also known as aorto-mitral continuity.
2. **Answer: C.** Severe concentric and septal hypertrophy may cause intracavitary gradients that are not correctable with valve replacement.
3. **Answer: A.** Isolated aortic insufficiency is usually a consequence of structural abnormalities of the valve, causing leaflet elongation and prolapse. This can occur in myxomatous degeneration and connective tissue disorders.
4. **Answer: E.** Aortic insufficiency has an insidious onset characterized by the gradual development of congestive heart failure and fatigue. Angina and syncope are rare.
5. **Answer: B.** In addition to providing excellent postoperative hemodynamics, full aortic root replacement with the Medtronic free-style bioprosthesis has been shown to have nearly 100 percent freedom from aortic insufficiency and reoperation at 8 years.

# 33

# Aortic Root Replacement

*Kaushik Mandal*
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## KEY CONCEPTS

- Epidemiology
  - Aortic aneurysms were the 15th most common cause of death in the United States in the year 2000. Among patients who die of thoracic aortic aneurysms (TAAs), rupture is the cause of death in about 80 percent of cases. Approximately 50 percent of thoracic aneurysms involve the root and the ascending aorta. The estimated growth rate for TAAs has been calculated to be 1.2 to 4.2 mm/year. Aneurysms that are larger than 6 cm can be associated with a yearly rate of rupture or dissection of at least 6.9 percent and a death rate of 11.8 percent.
- Pathophysiology
  - Annuloaortic ectasia is a term used to describe an increase in diameter of the aortic annulus coupled with an increase in the diameter of the aortic root. This type of situation is seen in patients with Marfan syndrome, Ehlers–Danlos syndrome, Loeys–Deitz syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum. Annuloaortic ectasia may have familial origins or may be idiopathic. Recently, a significant body of research has focused on the involvement of endogenous extracellular matrix-degrading enzymes in aneurysms and aortic remodeling. Of greatest interest are the matrix metalloproteinases (MMPs), particularly those of the gelatinase class (MMP-2, MMP-9). Similarly ARB2 receptor blockade with Losartan has shown to slow the dilatation of aorta in animal model studies. Another important cause of aortic root destruction is acute infective endocarditis with aggressive organisms such as *Staphylococcus aureus*. A central common theme in the development of aortic root aneurysms is cystic medial degeneration, in which gradual disruption of the media of the aorta occurs, with the creation of small acellular spaces within it. This process weakens the aortic wall, and a slow remodeling of the aortic root and ascending aorta results in aneurysm formation.
- Clinical features
  - Most patients with aortic root pathology are asymptomatic, with the exception of patients who present with endocarditis (sepsis, congestive heart failure) or aortic root destruction secondary to acute type A aortic dissection (severe chest pains, asymmetric pulses, congestive heart failure). The age range of presentation is very broad (twenties to eighties) and is dependent on the underlying pathology. Certain patients will have characteristic stigmata of connective tissue diseases such as Marfan syndrome.
- Diagnostics
  - The workup for candidates for aortic root replacement includes echocardiography to estimate ventricular function and assess for the possibility of aortic valve preservation. Coronary catheterization is usually necessary to rule out coronary artery disease. Thin-slice computed tomography (CT) or magnetic resonance imaging (MRI) scanning will provide the necessary information about the anatomy of the aneurysm. A careful oral examination or dental consultation is very important to prevent postoperative prosthetic valve infection.
- Treatment
  - Aortic root replacement options include composite valve-graft, separate valve-graft, xenograft tissue, homograft, pulmonary autograft (Ross procedure), and valve-sparing aortic root replacement. The decision to use each one of these options is dependent on patient age and valve preference, comorbid conditions, the condition of the native aortic valve, and contraindications to the use of anticoagulants.
- Outcomes
  - Operative (30-day) mortality runs in the range of 0 to 10 percent. Reoperation for mediastinal hemorrhage should be required in less than 10 percent of cases. Complete heart block requiring pacemaker insertion occurs in about 1 to 2 percent in most series. Stroke occurs in approximately 1 to 4 percent of these patients. Approximately 30 percent of patients who present for aortic root replacement are candidates for a valve-sparing procedure that offers improved freedom from bleeding and thromboembolic complications and obviates the need for oral anticoagulation.

## BACKGROUND

The first thoracic aortic replacements were performed with homograft tissue primarily in the descending thoracic aorta. Continuing efforts at developing an artificial fabric graft for use for aortic replacement, culminated with Michael DeBakey's discovery of Dacron.[1] During the late 1950s, the Houston group led by Michael DeBakey systematically developed operations for resection and graft replacement of the ascending aorta, followed by the descending and thoracoabdominal aorta. In 1968, Bentall and DeBono published a landmark article on replacement of the entire aortic root with anastomoses of the coronary ostia to the replacement graft.[2] The description of this technique included side-to-side anastomoses of the coronary arteries to the graft. The aneurysm sac then was closed completely around the graft. A common complication of this operation was pseudoaneurysmal development at the level of the coronary ostia, presumably caused by the tension placed on the coronary anastomoses. A subsequent modification of this technique by Kouchoukos and coworkers[3] included complete excision of the aneurysm and aortic root, leaving both coronary arteries suspended by only a small "button-shaped" circular portion of aorta that then would be anastomosed directly into a hole created in the side of the Dacron graft, thus eliminating pseudoaneurysm formation. An extended ascending aortic replacement was described by Wheat and associates, effectively excluding most of the ascending aorta but leaving the coronary arteries attached to the remaining aortic root tissue in continuity.[4]

In 1979, acting on the observation that many patients presenting for aortic root replacement have normal aortic valve morphology, Sir Magdi Yacoub and colleagues at Harefield Hospital in the United Kingdom developed a strategy for aortic root replacement in which the aortic valve was preserved.[5] In 1988, Tirone David introduced a different technique for valve-sparing aortic root replacement.[6]

Interest in homograft aortic root replacement began in the 1950s. At that time, Norman Shumway and colleagues at Stanford University were experimenting with excision of the right ventricular outflow tract, the pulmonary valve, and the proximal portions of the pulmonary artery in continuity in dogs and translocating this to the aortic root, with subsequent reconstruction of the pulmonary artery with homograft or tube graft material.[7] The operation in this iteration ultimately would be doomed to failure because of right ventricular failure resulting from the lack of a pulmonary valve, but Donald Ross, building on that experience, later performed the first pulmonary autograft aortic root replacements in humans.[8]

## DEVELOPMENTAL ANATOMY

The aortic root and the ascending aorta develop as part of a common truncus arteriosus that partitions itself into the ascending aorta and the aortic root and the pulmonary artery at approximately the fifth and sixth weeks of development. The aortic root is a tripartite structure owing to the presence of coronary sinuses. The aortic valve proper has no true fibrous annulus, although surgeons use the term *aortic annulus* to describe the junction of the aorta and the ventricle. The noncoronary sinus of the aortic valve tends to be the largest of the three sinuses, and therefore the size of the aortic valve leaflets reflects this, with the noncoronary leaflet generally being the largest. The length of the distance from the basal attachment of each aortic valve leaflet to the aorta is approximately 1.5 times the length of the free margin of the leaflet (Fig. 33-1). The commissures of each of the aortic valves extend right to or just below the sinotubular junction that marks the anatomic ridge between the end of the aortic root and the beginning of the ascending aorta. In general, the sinotubular ridge is approximately 10 to 15 percent smaller in diameter than the aortic annulus (Fig. 33-1). Anatomic disease states that cause dilatation of the sinotubular junction or dilatation of the aortic annulus will cause insufficiency of the aortic valve. There is an aortic–mitral continuity, which is a fibrous tissue attachment between the aorta and the mitral valves that constitutes approximately 55 percent of the circumference of the aortic root. The left side of the aortic root toward the pulmonary artery is attached to the ventricular muscle, corresponding to approximately 45 percent of the circumference.

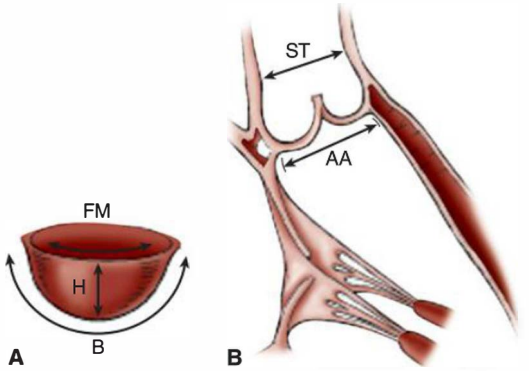



**FIGURE 33-1** Anatomic features of the aortic root. **A.** Normal aortic valve leaflet. **B.** Aortic root demonstrating the smaller diameter of the sinotubular junction compared with the aortic annulus. (Reproduced with permission from David TE. Complex operations of the aortic root. In: Edmunds LH (ed). *Cardiac Surgery in the Adult*. New York: McGraw-Hill, 1997:939–957.)

## EPIDEMIOLOGY

The exact extent of occurrence of thoracic aortic aneurysms (TAAs) is unknown. Bickerstaff and associates[9] found the prevalence of TAAs to be 5.9 per 100,000 per year in the Rochester, MN, area. Among a total of 72 patients with TAAs studied by Bickerstaff and colleagues, 51 percent, or 37 of the aneurysms in those patients, involved

the ascending aorta, 8 (11 percent) the aortic arch, and 27 (38 percent) the descending thoracic aorta.

According to the National Center for Health Statistics, aortic aneurysms (AAs) were the 15th most common cause of death in the United States in the year 2000; approximately 0.6 percent of all females and 1.1 percent of all males die of aortic aneurysmal disease. TAA deaths occur in about 0.7 per 100,000 population per year.[10] Among patients who die of TAAs, rupture is the cause of death in about 80 percent of cases.

The estimated growth rate for TAAs has been calculated to be 1.2 to 4.2 mm/year, and enlargement accelerates as an aneurysm gets larger.[11] Risk factors for accelerated growth include the presence of dissection in the enlarged segment, synchronous arch or abdominal AA, smoking, no β-blocker therapy, renal failure, and diastolic hypertension. Rupture is much more likely to occur when the aneurysm exceeds 5 cm in diameter, and the risk of rupture increases as the aneurysm increases in size. Aneurysms larger than 6 cm can be associated with a yearly rate of rupture or dissection of at least 6.9 percent and a death rate of 11.8 percent.[12]

## PATHOPHYSIOLOGY

*Annuloaortic ectasia* is a term used to describe an increase in the diameter of the aortic annulus coupled with an increase in the diameter of the aortic root. This ectasia tends to occur along the fibrous tissue of the ventricle, with the ventricular muscular portion of the aortic root generally preserved. This type of situation is seen in patients with Marfan syndrome (characterized by defect in the fibrilin gene), Ehlers–Danlos syndrome (characterized by a defect in type 3 collagen synthesis), Loeys–Dietz syndrome (characterized by a defect in Transforming Growth Factor beta gene), osteogenesis imperfecta, and pseudoxanthoma elasticum. It may have other familial origins or may be idiopathic. In these syndromes, the aortic sinuses become thinner and dilated and the sinotubular junction increases in diameter. When this happens, the aortic valve leaflets are not allowed to coapt properly because of separation of the commissures. These patients develop central jets of aortic insufficiency on echocardiographic assessment. Degenerative diseases of the aorta may cause dilatation of the ascending aorta and aortic sinuses with minimal or no dilatation of the aortic annulus. The aortic root also may be destroyed in the setting of acute or chronic aortic dissection and other congenital syndromes, such as those associated with bicuspid aortic valves. Recently, a significant body of research has focused on the involvement of endogenous extracellular matrix degrading enzymes in the involvement of aneurysms and aortic remodeling. Of greatest interest are the matrix metalloproteinases (MMPs), particularly those of the gelatinase class (MMP-2, MMP-9).[13,14] Another important cause of aortic root destruction is acute infective endocarditis with aggressive organisms such as *Staphylococcus aureus*.

A central common theme in the development of aortic root aneurysms is a condition referred to as cystic medial degeneration or simply medial degeneration. Histologically, the aorta is made up of three layers. The adventitia is composed primarily of a collagen-rich network. The tunica media, or media, is composed of alternating layers of vascular smooth muscle and elastin. Each successive pairing of smooth muscle cells and elastin is referred to as a lamellar unit. In humans, the media of the aortic root is composed of approximately 50 lamellar units. The third layer of the aorta is referred to as the intima and is composed of a single layer of epithelial cells. In many cases of AA, one sees gradual disruption of the media of the aorta, with the creation of small acellular spaces within it. This process of medial degeneration results ultimately in weakening of the aortic wall and inability to sustain the normal shear stresses associated with systole. As a result, a slow remodeling of the aortic root and ascending aorta occurs, leading to aneurysm formation.

## CLINICAL PRESENTATION AND DIAGNOSTIC MODALITIES

Patients present for aortic root replacement in a number of circumstances (see the decision-making flowchart; Fig. 33-2). The most acute circumstance is a patient with a Stanford type A aortic dissection in whom the aortic root is virtually destroyed by the proximal extent of the dissection. The condition of these patients constitutes a surgical emergency, and as a result, aortic root replacement in these circumstances is associated with more morbidity and a higher mortality than is standard aortic root replacement. A second acute situation occurs with infective endocarditis. The most common situation in which patients present for aortic root replacement is an aortic root aneurysm. The age range of presentation is wide and starts in the 20s and 30s in patients with hereditary connective tissue disorders and extends into the 70s and even 80s in those with degenerative aneurysms. Other than a family history of AAs and connective tissue disorders, risk factors for AAs include hypertension and atherosclerosis. Patients with isolated aortic root aneurysms are usually asymptomatic. Those conditions are identified as a result of a workup for another disease process, such as a respiratory tract infection, that results in a chest x-ray. The chest x-ray may identify an abnormality in the mediastinum, resulting in a computed tomography (CT) scan or a magnetic resonance imaging (MRI) scan that illustrates the aortic root aneurysm. Alternatively, other patients with AAs have significant aortic valve pathology, such as stenosis or insufficiency. Symptoms from these conditions result in referral to a physician. An echocardiogram is performed and shows evidence of aortic stenosis or insufficiency, and often a dilated aortic root is identified. This often leads to a further imaging study, such as a CT scan or an MRI scan, which shows the aortic root aneurysm.

The workup in patients with an aortic root aneurysm involves a careful history and physical examination, assessing for a history of bleeding problems and a history of significant dental work. In addition, a family history of AA

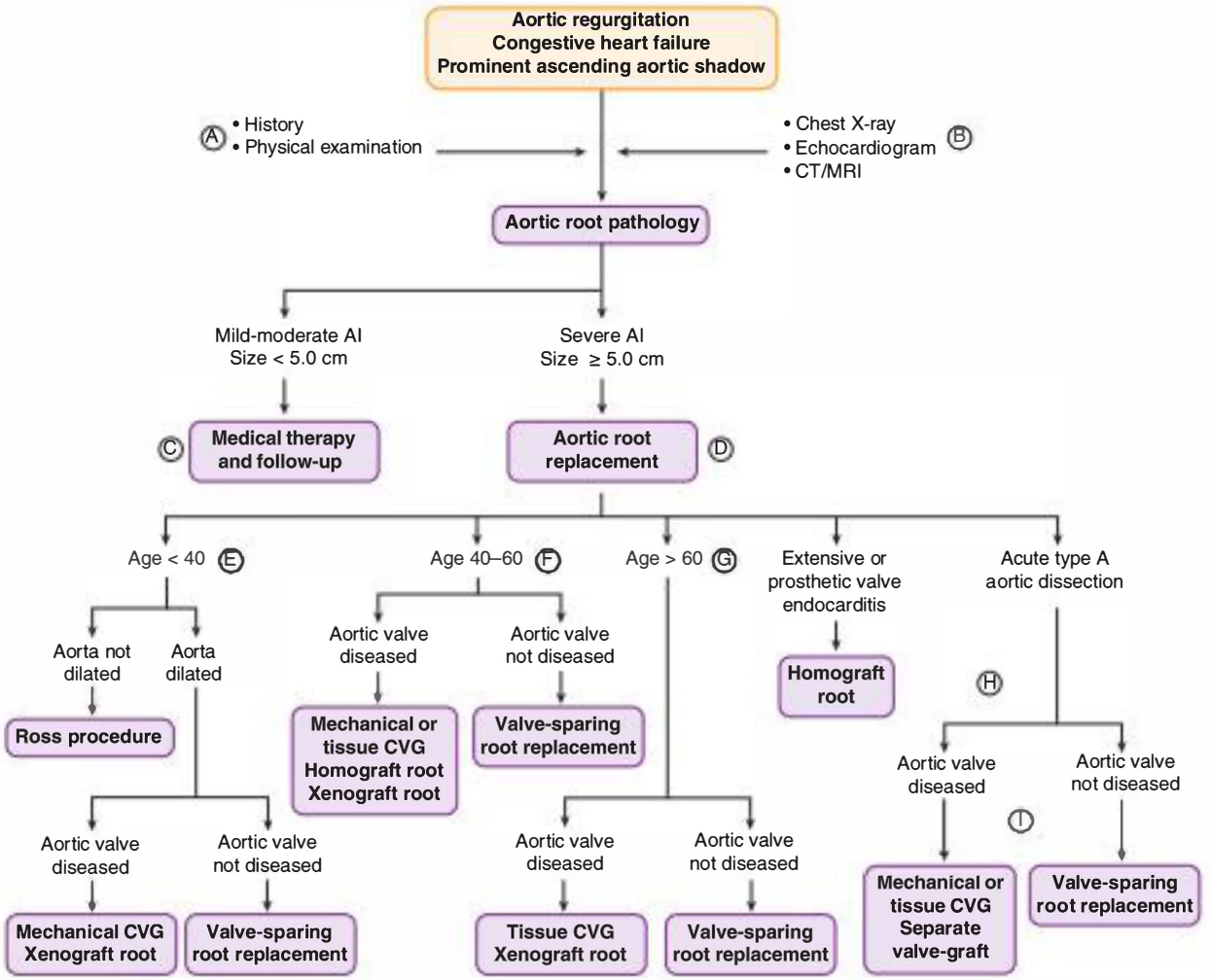



**FIGURE 33-2** Decision-making flowchart: Aortic root replacement.

should be elicited. The physical examination is generally unremarkable apart from the features of aortic insufficiency and aortic stenosis. Patients with Marfan syndrome have a very characteristic appearance. They tend to be tall and thin, with joint laxity, pectus excavatum, and very characteristic facial features. After physical examination, patients should have standard blood work and be crossed and typed for 4 to 6 units of red blood cells. Clotting studies should be performed. The electrocardiogram shows no abnormalities specific to the aortic root aneurysm. Chest x-ray often reveals a prominent right mediastinal border, which represents an outpouching of the aortic root and the ascending aorta into the right chest. Transthoracic echocardiography is valuable in showing features of aortic stenosis and aortic insufficiency in addition to allowing assessment of the potential for valve preservation. The most useful test for the evaluation of aortic root aneurysms is a contrast CT scan or MRI, especially scans with three-dimensional reconstructions; this allows precise assessment of the aortic root and its dimensions (Fig. 33-3). Females older than 40 years and males older than 35 years with coronary risk factors should undergo coronary angiography to rule out the presence of coronary artery disease before surgery. In addition, patients with significant neck bruits should have carotid vascular studies and those with a substantial history of smoking should have pulmonary function tests. Finally, a dental examination is critical whenever a prosthetic valve replacement is considered in a patient since bacterial seeding from dental disease is a very important cause of prosthetic valve endocarditis (PVE) and graft infections.

## MEDICAL THERAPY

At the present time, there is no medical therapy for aortic root dilatation that directly addresses the underlying etiology. Some treatment strategies have focused on the use of broad-spectrum MMP inhibitors to reduce or prevent aneurysm

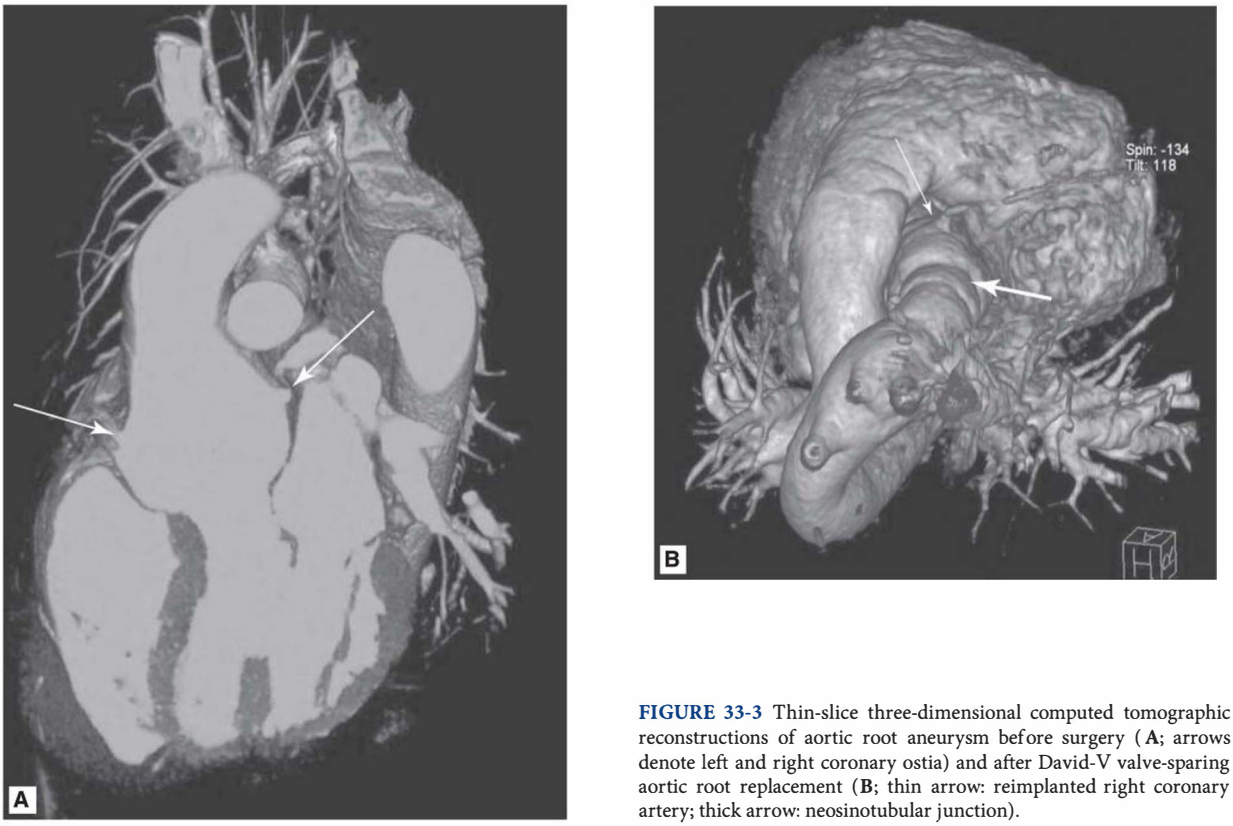



**FIGURE 33-3** Thin-slice three-dimensional computed tomographic reconstructions of aortic root aneurysm before surgery (**A**; arrows denote left and right coronary ostia) and after David-V valve-sparing aortic root replacement (**B**; thin arrow: reimplanted right coronary artery; thick arrow: neosinotubular junction).

expansion. Thompson and Baxter gave doxycycline 100 mg twice a day for 7 days to five patients before abdominal AA repair, and aneurysm biopsy showed a three-fold reduction in MMP-2 and a four-fold reduction in MMP-9 expression compared with nontreated controls in whom those two enzymes were expressed abundantly.[15] After this, a multi-institutional phase II prospective randomized trial was undertaken to assess the safety and potential efficacy of long-term doxycycline administration in 36 patients. Thirty-three patients completed the study, and significant treatment-related side effects occurred in five, or 13.9 percent, of those patients. There was no significant increase in aneurysm size at 6 months, and plasma MMP-9 levels dropped so that only 21 percent of the patients in the drug arm had MMP-9 that was considered to be elevated compared with 47 percent in the control arm.[16] Recent work from our institution has similarly suggested a role for ARB2 blocker Losartan, in slowing the growth of thoracic aneurysms associated with Loeys–Dietz Syndrome.[17] Hence, at present, the mainstays of management of aortic root aneurysms are judicious hypertension control using a combination of β-blockers and ARB2 receptor blockers in conjunction with regular follow-up with CT scans and transthoracic echocardiography to assess for interval changes in aortic diameter and follow the characteristics of the aortic valve.

## INDICATIONS FOR SURGERY

Generally, resection of an aortic root aneurysm is indicated in patients in whom the aortic root diameter exceeds 5 to 5.5 or becomes twice the size of a comparable normal aortic segment.[11] In addition, a patient with an aortic root aneurysm that is seen to grow more than 0.5 cm in a 6-month period also should be considered for operation. Some latitude is given for patients with connective tissue disorders in whom it is known that the aorta is inherently weak and more susceptible to rapid dilatation, especially in patients with Loeys–Dietz syndrome (ascending aortic diameter cutoff 4 cm), those with bicuspid aortic valve (ascending aortic diameter cutoff 4.5 cm), and those with Marfan (ascending aortic diameter cutoff 5 cm). The clinical situation often also arises when patients have significant aortic valve pathology in association with an AA that does not quite meet the size criteria for resection. In these circumstances, aortic root replacement is indicated, since isolated replacement of the aortic valve in patients with a large aortic root and ascending aorta can pose technical difficulties in terms of closing the aorta after the aortic valve procedure and may predispose those patients to aortic dissections. In addition, a complicated redo operation for aortic root replacement may be necessary, since the ascending

aorta continues to dilate. As was stated earlier, aortic root replacement occasionally is indicated in patients with type A aortic dissections with destruction of the aortic root and also in younger patients with significant aortic valve pathology who have a normal aortic root and ascending aorta and who are undergoing homograft root replacement or a Ross procedure to benefit from the increased durability of the aortic valve associated with this operation. Finally, severe aortic valve endocarditis with abscess or PVE may be best treated with homograft aortic root replacement.

# SURGICAL THERAPY

## Conduct of the Operation

The patient is placed in the supine position under general anesthesia. The chest, abdomen, perineum, and lower extremities are prepped and draped in sterile fashion. Standard median sternotomy and exposure of the heart are performed. The orientation of the aortic root is visualized more easily if only the right side of the pericardium is tacked upward. This rotates the heart counterclockwise and allows the apex of the heart to sink into the left chest, thus improving the exposure of the aortic root. Arterial and venous cannulation is undertaken, and appropriate connections are made to the pump oxygenator. If the patient has no significant aortic insufficiency, an antegrade cardioplegia tack is placed, and in all cases a retrograde cardioplegia cannula also is placed. When everything is in readiness for the initiation of cardiopulmonary bypass, careful dissection is undertaken to separate as much of the aortic root from the pulmonary artery and right ventricular outflow tract as possible. Care must be taken in dissecting anteriorly to avoid injury to the right coronary artery. A careful dissection at this point can result in significant exposure of the aortic root and therefore decrease the amount of time needed to perform the aortic root replacement when the aorta is cross-clamped. After confirmation of an activated clotting time (ACT) longer than 400 s, cardiopulmonary bypass is performed and the aorta is cross-clamped. Whenever possible, the heart should be arrested with antegrade cardioplegia to promote better and faster distribution of the cardioplegia. A switch to retrograde cold blood cardioplegia may be considered especially in the presence of significant aortic regurgitation. The authors give intermittent shots of 250 mL every 20 min during the cross-clamp period. This is supplemented with a cold saline-infused cooling jacket placed around the left ventricle. A right superior pulmonary vein vent is placed to keep the heart decompressed.

The ascending aorta is transected approximately 3 to 4 cm above the right coronary ostium. The aortic valve is inspected at this point, and if the situation is appropriate for valve preservation, the valve is not excised. If the valve is diseased so that its successful preservation is not possible, it is excised and debridement of the annulus is carried out if necessary. At this point, both the left and the right coronary buttons are dissected free, taking care not to mobilize them significantly. Significant mobilization may result in disorientation and kinking of the button after anastomosis to the Dacron graft. Specific techniques and choices for aortic root replacement are discussed below.

Systemic rewarming is begun at an appropriate point in the implantation procedure to avoid imposing extra time waiting for the patient to reach normothermia before separation from cardiopulmonary bypass. After root replacement, the vent is removed, and it is useful to give the final shot of cardioplegia antegrade to inspect for significant bleeding points that can be repaired before removal of the cross-clamp and also as an initial test of valve competence. The cross-clamp is removed with the patient placed in the Trendelenburg position and with an ascending aortic vent on. Ventricular and atrial pacing wires are placed, and mechanical ventilation is resumed. De-airing maneuvers such as lung hyperinflation, side-to-side shaking of the chest, and manual agitation of the heart are performed with the heart partially ejecting. Transesophageal echocardiography is very helpful in the assessment of de-airing and also in the interrogation of the valve for correct leaflet function. The patient is weaned from bypass at a systemic temperature of 36.5 to 37°C with good ventilation parameters. Protamine is given slowly, and the patient is decannulated. Meticulous hemostasis is obtained, a midline mediastinal drain (36F thoracostomy tube) is placed, and the patient is closed in the standard fashion.

## Aortic Root Replacement: Choices and Results

### COMPOSITE VALVE-GRAFT

The current gold standard for aortic root replacement is the composite valve-graft replacement. Typically this consists of a mechanical valve that is annealed to a double-velour woven Dacron graft at the factory. The most commonly used version is the St. Jude composite valve-graft, although other brands are available. The operation consists of removal of the aortic root in its entirety except for the coronary ostia that are left surrounded by a small circular rim of native aorta. The aortic valve also is excised. After appropriate sizing, pledgeted horizontal mattress nonabsorbable sutures are placed across the annulus in everting fashion (i.e., from aorta to ventricle) and are placed across the sewing ring of the composite valve-graft. The composite valve-graft is seated, and the sutures are tied and cut. For an extra measure of hemostasis, it is useful to suture the remaining rim of the aortic root directly to the sewing ring of the composite valve-graft in running fashion with 3-0 polypropylene sutures. Small holes are made just above the valve in the graft with ophthalmic cautery to allow suture implantation of the right and left coronary buttons. The authors use a small amount of albumin–glutaraldehyde biological glue to seal the interstices of these suture lines to aid in achieving hemostasis, but with the understanding that this step is not a substitute for meticulous surgical technique. A distal anastomosis of the Dacron graft to the ascending

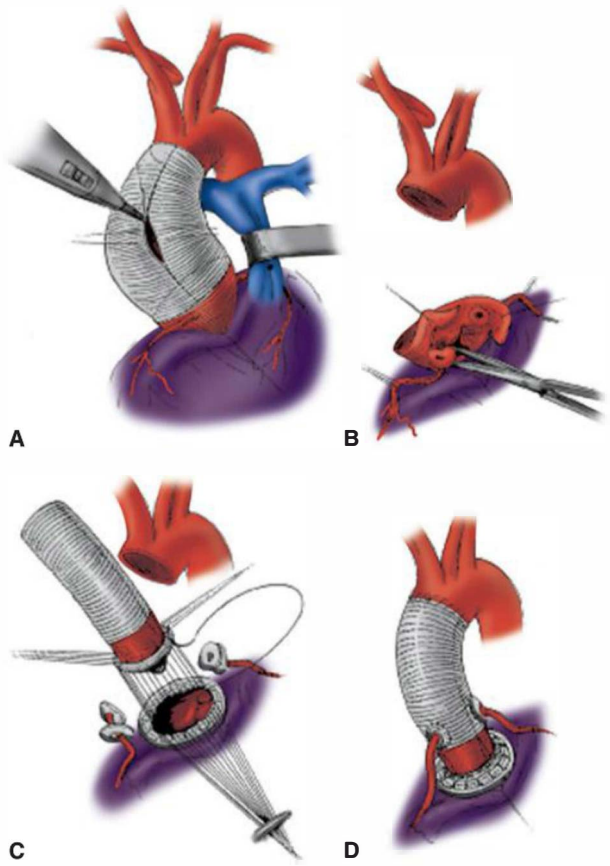



**FIGURE 33-4** Insertion of a composite graft with the button technique. The aorta is opened vertically (**A**), and the coronary ostia are mobilized sufficiently (**B**) before the valve is seated (**C**). The coronary buttons are sewn to the graft (**D**) to complete the repair. (Reproduced with permission from Svensson LG, Crawford ES. Aortic dissection and aortic aneurysm surgery: Clinical observations, experimental investigations, and statistical analyses: Part III. *Curr Probl Surg* 1993;30:1–72. Copyright Elsevier.)

aorta then is performed (Fig. 33-4). In the operation originally described by Bentall and Debono in 1968,[2] the aortic root was not excised and the coronary ostia were sewn side to side to the Dacron graft. Subsequently, Kouchoukos and coworkers excised the native aorta, leaving the coronary ostia surrounded by a small circular rim of native aorta ("Carrel buttons") for direct end-to-side reimplantation.[3] This constitutes the standard operation performed today. It is therefore not academically appropriate to refer to the latter procedure simply as a Bentall operation; instead, it is a modification of that operation.

Younger individuals may opt for a replacement of a composite graft containing a mechanical valve, accepting the potential complications associated with warfarin administration. In older patients (i.e., those above 65–70 years of age) a composite graft consisting of a stented bioprosthetic valve sewn to the Dacron graft by the surgeon at the time of operation may be used. Although these valves are not commercially available, the surgeon can select the appropriate bioprosthetic valve by sizing the annulus after the native valve is excised and then suture it to an appropriately selected Dacron graft. The operation then proceeds as for a composite mechanical valve graft.

During redo aortic root replacements, the tissues around the aortic root, especially posteriorly, can be very difficult to dissect; therefore, mobilization of the coronary artery may be difficult or dangerous. The Cabrol technique[18] of coronary reimplantation involves the placement of 8- or 10-mm tube grafts to each coronary ostium with a side-to-side connection to the main aortic graft (Fig. 33-5). This procedure can be complicated by kinking of the right or left limb of the side graft if it is not oriented correctly in addition to the long-term risk of right coronary artery occlusion. An alternative approach involves direct reimplantation of the right coronary button (which almost always can be mobilized sufficiently) and reimplantation of the left coronary artery with an interposition graft between the aortic graft and the left coronary ostium.

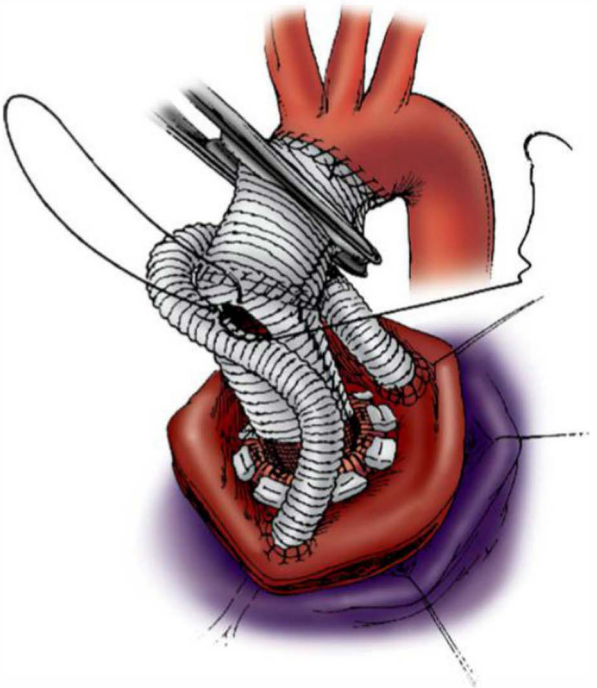


**FIGURE 33-5** Composite valve-graft insertion with the Cabrol technique. The tube graft to the left main ostium is brought behind the composite graft, and the composite graft is sutured to the aortic arch or to the graft that has been used for arch replacement. Finally, the coronary interposition graft is sutured to the right coronary artery ostium and the anastomosis (side-to-side) is completed. (Reproduced with permission from Svensson LG, Crawford ES. Aortic dissection and aortic aneurysm surgery: Clinical observations, experimental investigations, and statistical analyses: Part III. *Curr Probl Surg* 1993;30:1–72. Copyright Elsevier.)

The results of composite valve-graft aortic root replacement operations are generally very good but are dependent on the indication for operation. Gott and associates reviewed the extensive experience at Johns Hopkins with aortic root replacement in Marfan syndrome patients over a 24-year period.[19] Two hundred thirty-five Marfan patients underwent elective aortic root replacement with no 30-day mortality. The actuarial freedom from thromboembolism, endocarditis, and reoperation on the residual aorta 20 years postoperatively was 93 percent, 90 percent, and 74 percent, respectively. Lai and associates reviewed the Stanford experience with composite valve-graft (CVG) replacement for acute type A aortic dissection.[20] Thirty-day, 1-year, and 6-year survival estimates of 86 ± 8, 81 ± 9, and 65 ± 16 percent were seen with composite valve-graft replacement, with a 6-year freedom from reoperation of 100 percent. Ehrlich and coworkers[21] reported on 84 patients older than 65 years of age (median age was 74 years with a range of 66 to 89 years) who underwent CVG aortic root replacement over an 11-year period. Hospital mortality was 8.3 percent (7 of 84), with 16 late deaths (19 percent) noted during a median follow-up of 3.2 years (range 0 to 10 years). The authors concluded that composite valve-graft replacement in elderly patients results in low operative mortality, has excellent long-term survival, and averts fatal aneurysm rupture even in that higher-risk population.

## THE COMPOSITE VALVE-GRAFT VERSUS SEPARATE VALVE-GRAFT CONTROVERSY

In many cases an acceptable alternative to full CVG aortic root replacement is ascending aortic replacement starting at the sinotubular junction in association with separate aortic valve replacement [separate valve-graft (SVG)], leaving an intervening segment of the patient's own aortic root from which the coronary ostia originate. The SVG procedure is less technically demanding and is useful when the sinotubular junction is not effaced and the aortic root is not dilated. It is useful in elderly patients in whom a shorter cross-clamp time may limit morbidity, especially those with acute type A without significant annuloaortic ectasia. A relatively common problem is significant ascending aortic dilatation associated with aortic valve replacement for a bicuspid aortic valve. It is well known that patients with bicuspid aortic valves are predisposed to the development of ascending and root aneurysm. The cause is multifactorial and includes hemodynamic factors and heredity.[22]

McCready and associates[23] observed an approximately 15 percent incidence of significant root dilatation an average of 6.5 years after the SVG procedure. Houel and coworkers[24] found mortality rates of 7.7 percent with CVG versus 11 percent with SVG ($p$ = not significant). Actuarial survival at 10 years postoperatively in these groups was 77.7 ± 5.6 versus 75.8 ± 6.9 percent ($p$ = not significant). However, freedom from late complications of the ascending aorta was significantly different (97.3 ± 1.9 percent CVG versus 68.3 ± 9.0 percent SVG at 10 years postoperatively). The SVG technique was identified as a risk factor for late complications of the ascending aorta by multivariate analysis ($p = 0.01$; odds ratio 9). In light of these data, an aggressive approach to CVG replacement in this population is recommended in patients with acceptable risk.[25] When the sinotubular junction and aortic root are intact so that SVG is considered appropriate, the procedure first described by Wheat and associates[4] may be useful to maximize exclusion of as much native aortic root tissue as possible without incurring the extra technical challenge of a full CVG implantation. The decision to pursue CVG replacement to exclude all potentially diseased aortic root tissue should be tempered by an increased operative mortality rate compared with an isolated aortic valve replacement. The SVG technique may provide a reasonable compromise between these two procedural extremes, especially if concomitant procedures must be performed in the same setting; however, there is a risk of aneurysmal dilatation of the intervening aorta over time.

## STENTLESS VALVE AS AN ALTERNATIVE FOR AORTIC ROOT REPLACEMENT

The Freestyle aortic root bioprosthesis (Medtronic, Inc., Minneapolis, MN) is a stentless porcine aortic root prepared with low-pressure and zero-pressure fixation processes and α-aminooleic acid leaflet anticalcification treatment, with the aim of optimizing both hemodynamics and bioprosthesis durability. The device can be implanted as a subcoronary or modified subcoronary valve replacement, as a complete aortic root replacement (total root), or as a root inclusion. Initial implantations in human subjects began in 1992, and the device has been approved for clinical use in the United States since 1997. The implantation technique of this prosthesis is similar to that for CVG replacement described above. Bach and colleagues[26] reported the 8-year results of a multicenter cohort of 700 patients (of whom 93 percent were over 60 years of age) followed prospectively who received various configurations of this prosthesis. A total root replacement was performed in 162 of those patients, with actuarial freedom from valve-related death of 92.3 percent, freedom from structural deterioration of 100 percent, and freedom from moderate or more aortic regurgitation of 98.7 percent. Oral anticoagulation is not required postoperatively.

## HOMOGRAFT AORTIC ROOT REPLACEMENT

Aortic root replacement can be performed with a cryopreserved homograft aortic root. This operation is more technically demanding because of the less rigid nature of the tissue used. The operative technique is similar to the techniques described above except that many authors advocate a continuous running suture for the implantation of the left ventricular outflow tract side to the annulus. In addition, this proximal suture line must be planar; that is, it should not follow the scallops of the aortic annulus but should run somewhat under the commissures. This operation is particularly well suited for patients in the age range of 40 to 60 years

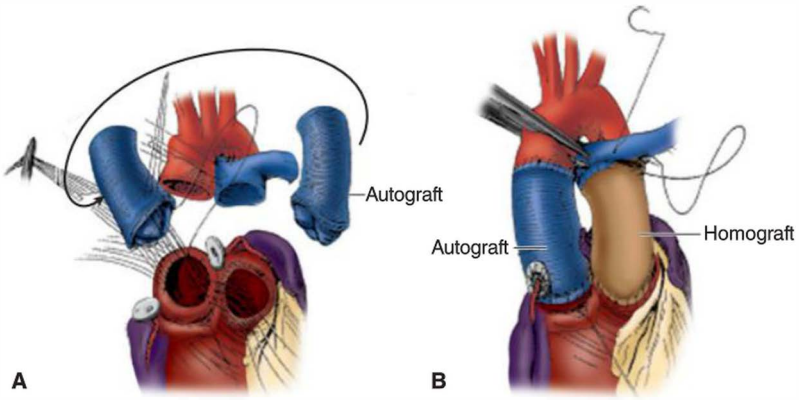



**FIGURE 33-6** Insertion of a pulmonary autograft into the aortic position (Ross procedure). The pulmonary autograft is seated in the aortic annulus with interrupted simple sutures (**A**). Attention is paid to ensure that the valve is properly seated, as the pulmonary valve does not have the differences in valve cusp edge lengths that the aortic valve has. The homograft is sutured into position in the native pulmonary outflow tract to complete the procedure (**B**). (Reproduced with permission from Svensson LG, Crawford ES. Aortic dissection and aortic aneurysm surgery: Clinical observations, experimental investigations, and statistical analyses: Part III. *Curr Probl Surg* 1993;30:1–72. Copyright Elsevier.)

(e.g., those with congenital bicuspid aortic valve pathology) who require aortic root replacement but do not wish to take oral anticoagulants. In addition, homograft root replacement is the operation of choice for extensive native and PVE. The analysis by McGiffin and associates[27] showed that the use of homografts in patients under 40 years of age was associated with an unacceptably high incidence of valve failure over a 15-year period. They demonstrated improved freedom from recurrent endocarditis when allograft tissue was used for aortic valve replacement compared with the use of prosthetic valve material. Grinda and colleagues[28] evaluated the short- and long-term results of cryopreserved aortic viable homograft (CAVH) in the treatment of active aortic endocarditis. One hundred four patients underwent CAVH replacement for active aortic valve endocarditis; 73 percent of those operations involved the native aortic valve, and 27 percent involved a prosthetic aortic valve. CAVHs were inserted using the aortic root replacement technique in 89 percent of those patients. Actuarial survival at 10 years was 83 percent, with 93 percent of the patients free from cardiac death. At 10 years, the actuarial rate for freedom from reoperation was 76 percent and that for freedom from recurrent endocarditis was 93 percent. No thromboembolic complications were observed.

## ROSS PROCEDURE

The Ross procedure consists of removal of the native aortic valve and root with preservation of the coronary buttons, followed by excision of the patient's own pulmonary valve encased in the pulmonary artery distally and a small rim of right ventricular outflow tract muscle proximal to the annulus. It is mandatory to rule out any abnormalities in the pulmonary valve (fenestrations) and significant mismatch in the size of the aortic root and right ventricular outflow tract before proceeding with the autograft explants. Close attention needs to be paid to any anomalous coronary artery crossing the right ventricular outflow tract and preserving the first septal branch of LAD as one proceeds with excision of the autograft. The pulmonary valve, after excision, is translocated to the aortic position as a root replacement, with sewing of the right ventricular muscle to the aortic annulus in a planar fashion, reimplantation of the coronary ostia, and a distal anastomosis between the pulmonary arterial end of the autograft and the ascending aorta. The right ventricle–pulmonary artery side then is reconstructed with a valved pulmonary homograft (Fig. 33-6). This procedure should be performed by surgeons who are extremely competent at aortic root operations. Although the procedure is very demanding technically, the results are outstanding, with 80 percent freedom from reoperation at 20 years,[29] with the failures roughly evenly distributed between the autograft and allograft sides. Recent reports have shown early dilatation of the autograft with neoaortic valve insufficiency (Fig. 33-7).[30] Histologic analysis shows evidence of medial degeneration in both the aorta (Fig. 33-8) and the pulmonary artery of patients with bicuspid compared with tricuspid aortic valves.[31] This is not surprising since embryologically the aorta and the pulmonary artery develop from a common truncus. Over time, gradual dilatation of the neosinuses of Valsalva is observed. This may be addressed by incorporation of aortic root stabilization adjuncts during the time of initial surgery.[32] In light of these data and given its technically demanding nature, many surgeons have tempered their enthusiasm for the Ross procedure and reserve it for young patients especially children who need a biologically viable root to achieve optimal growth.

## VALVE-SPARING AORTIC ROOT REPLACEMENT

Approximately 30 percent of patients who require aortic root replacement have a normal aortic valve that leaks because of

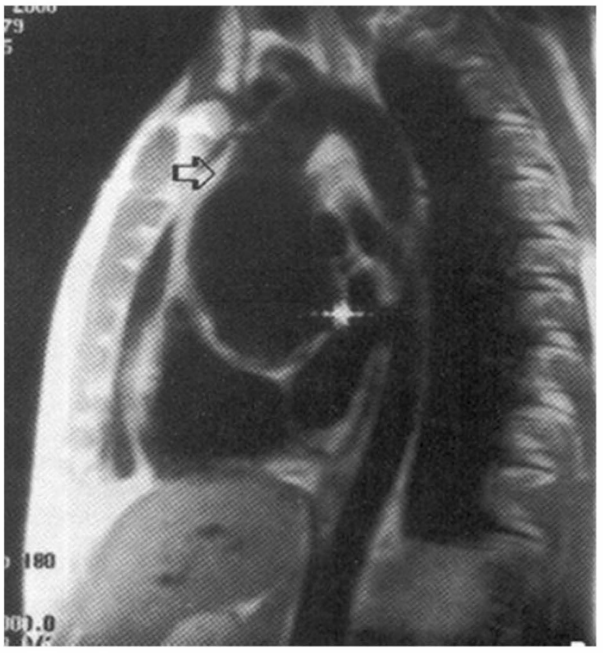


**FIGURE 33-7** Magnetic resonance image of the neoaortic root demonstrating dilatation of the pulmonary autograft and an abrupt transition to normal diameter at the distal suture line, as shown by the arrow. (Reproduced with permission from Sundt TM, Moon MR, Xu H. Reoperation for dilatation of the pulmonary autograft after the Ross Procedure. *J Thorac Cardio Surg* 2001;122(6):1249–1252. Copyright Elsevier.)

sinotubular junction effacement and/or aortic annular dilatation secondary to degenerative causes or connective tissue diseases such as Marfan syndrome. Rather than excising the aortic valve and replacing the root with prosthetic valve material, an operation that encloses the native valve within normal aortic root geometry should restore competency. In 1979, Sir Magdi Yacoub introduced an aortic valve-sparing root replacement ("remodeling," David-II) procedure consisting of excision of all the native aortic tissue except for a small rim around the valve leaflets.[5] An appropriately sized Dacron graft then is fashioned into three scallops at one end and sutured to the residual aortic tissue, followed by coronary reimplantation (Fig. 33-9).

In approximately 1988, Dr. Tirone David introduced the valve-sparing "reimplantation" (David-I) procedure,[6] in which sutures placed *proximal* to the aortic valve annulus are sewn to the Dacron graft. In this way, when the graft is seated, the valve sits entirely inside the graft and is attached to it from the inside with a second suture line after coronary reimplantation. The appropriate graft size is selected by measuring the average aortic valve leaflet height in millimeters, multiplying this value by 4/3, and adding 4 to 6 mm to this number to account for the thickness of the left ventricular outflow tract under the aortic annulus.[12]

The Yacoub remodeling procedure does not protect the aortic annulus and leaves it susceptible to dilatation and hence valvar insufficiency over time. David addressed this problem by placing a Teflon felt buttress under the fibrous portion of the annulus (David-III) but abandoned

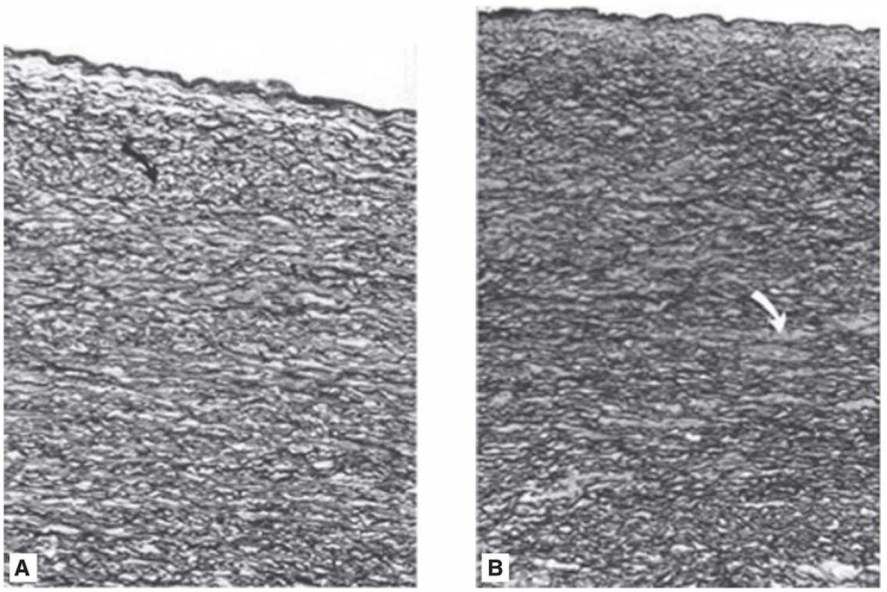



**FIGURE 33-8** **A.** Histologic features of aortic section from a patient with normal trileaflet aortic valve. There are no intimal changes. **B.** Histologic features of the ascending aorta from a 33-year-old patient with bicuspid aortic valve disease. Note the significant medial destruction and the accumulation of mucoid material (arrow). There is a marked fragmentation of elastic tissue. (Reproduced with permission from de Sa M, Moshkovitz Y, Butany T, David TE. Histological abnormalities of the ascending aorta and pulmonary trunk in patients with bicuspid aortic valve disease. *J Thorac Cardiovasc Surg* 1999;118(4):588–594. Copyright Elsevier.)



**FIGURE 33-9** Operative technique of the remodeling (Yacoub) valve-sparing aortic root replacement. (Reproduced with permission from Yacoub MH, Gehle P, Chandrasekaran V. Late results of a valve-preserving operation in patients with a neurysms of the ascending aorta and root. *J Thorac Cardiovasc Surg* 1998:115(5);1080–1089. Copyright Elsevier.)

that modification in favor of the reimplantation procedure. If reoperation is required because of valvar incompetence after the remodeling procedure, a full aortic root replacement is necessary because of the persistence of unprotected native aortic root tissue. In contrast, with the David reimplantation procedure, the entire aortic root and annulus are enclosed in graft material, preventing dilatation over time. If reoperation is required, the graft can be opened, the native valve can be excised, and a stented or stentless valve of choice may be sutured directly into the graft, obviating the need for a much more difficult root re-replacement.

With the original David operation, isolated case reports described native valve failure with fibrotic, retracted aortic leaflets seen at reoperation, perhaps consistent with repeated trauma to the leaflets secondary to the lack of "neosinuses" produced with the Yacoub procedure.[33] The David procedure has undergone two iterations to address this issue. The first (David-IV) involved the selection of a graft 4 to 6 mm larger in diameter than the calculation dictates and plication of the neosinotubular junction down to the correct size. With the current (David-V) modification, the Dacron graft used for the aortic root replacement is oversized by 6 to 8 mm in diameter and then pleated at the annular and new sinotubular junction.[34] The graft will billow outward when it is subjected to arterial pressure, thus creating neosinuses. At Hopkins (Fig. 33-10), we use a modified David I reimplantation procedure using the Valsalva graft, which has prefashioned pseudosinuses.[35] Our procedure differs from the original David I reimplantation technique in that only three subannular sutures are placed. The subannular sutures serve only to anchor the base of the graft below the annulus, holding the entire aortic valve complex within the graft and are not hemostatic. We believe that use of the Valsalva graft in a reimplantation procedure provides both annular stabilization and preservation of sinuses. The size of the graft is based on optimal sinotubular junction sizing using valve sizers, determined intraoperatively after transection of aorta. A graft that is 2 to 3 mm larger is chosen as the graft will sit outside the aortic valve complex. Most patients in our experience[35] have had optimal sinotubular junction diameters of 28 to 30 mm and end up receiving a 30- to 32-mm graft. We have not found that measurement of leaflet dimension and formulas for graft selection are useful. The Valsalva graft is available in sizes 24 to 34 mm, which can accommodate majority of aortic roots encountered in clinical practice. Although patients with annular diameters greater than 34 mm may undergo valve sparing root surgery, in our experience, these patients typically have thin, stretched out abnormal leaflets and often have severe valvular regurgitation. Surgeon experience and patient selection are important factors for good outcomes after VSRR. Modified Bentall operation still remains the procedure of choice in patients with severe regurgitation, leaflet asymmetry, and fenestrations and those having bicuspid valves with significant thickening or prolapsed.

The results of the David operation have been excellent, with 100 percent freedom from reoperation in Dr. David's hands.[36] Similar excellent results have been reported by other investigators.[35] Patients benefit from the long-term durability associated with preservation of their own valves, and anticoagulation is not required postoperatively.[35,36]

## Postoperative Care and Surgical Results

Immediate postoperative care should focus on control of hypertension (for which intravenous sodium nitroprusside is used most commonly) and maintenance of adequate filling pressures (central venous pressure 10–15 mm Hg, pulmonary capillary wedge pressures in the range of 15–18 mm Hg). Dual-chamber pacing is required in a small proportion of patients who leave the operating room in conduction block. Often this resolves within 24 to 48 h. If conduction block persists longer than 4 to 5 days, permanent pacemaker insertion should be considered. In patients with no conduction disturbances, pacemaker wires can be removed on the third or fourth postoperative day. The patient should be placed

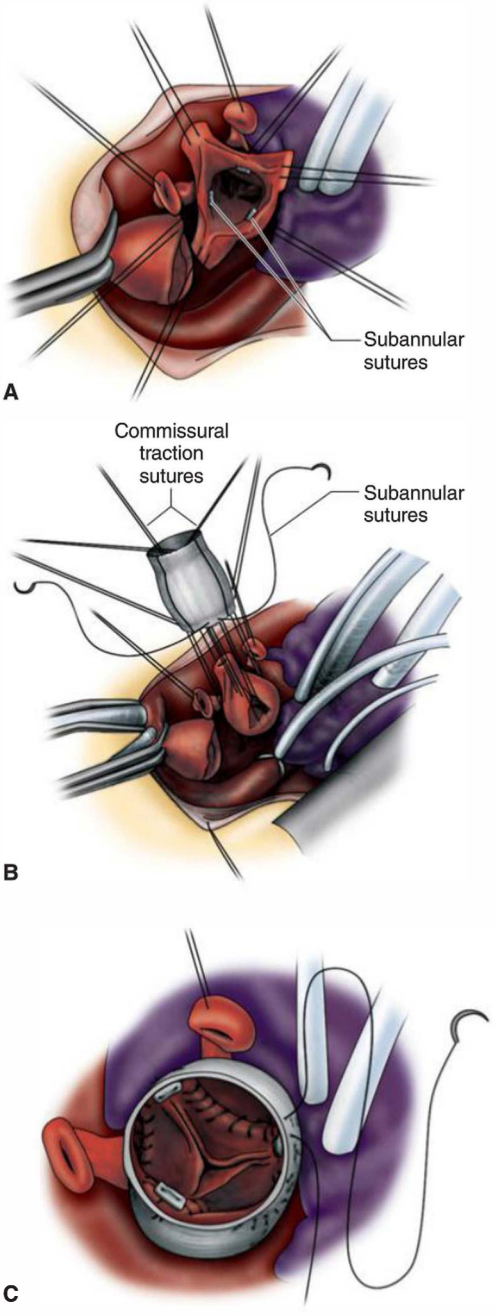



**FIGURE 33-10** Reimplantation (David-I) valve-sparing aortic root replacement- the Hopkins modification. **A.** Stay sutures are placed above each coronary artery, and the sinuses are excised, leaving a 4- to 5-mm sinus remnant attached to the annulus. The coronary arteries are widely mobilized; the dissection remains close to the annulus rather than the coronary to avoid "button-holing" the undersurface of the coronary artery. The area of fibrous continuity between the aorta and pulmonary artery should be separated down to a level flush with the nadir of the right sinus annulus. Some dissection of right ventricular muscle from the aorta at the anterior (right-noncoronary) commissure is sometimes necessary, but one should avoid overzealous use of the cautery here, as our only case of permanent heart block necessitating a permanent pacemaker resulted from a thermal or electrical injury to the AV node during this dissection. In our technique, pledgetted mattress sutures of 2-0 Tevdek are placed about 2 mm below the nadir of the annulus in each of the three sinuses; only two subannular sutures are used if a bicuspid valve is present. The mattress suture should not be too wide, as it may distort the base of the leaflet. If the surgeon prefers, additional subannular sutures can be placed but our experience suggests they are rarely necessary, as the bottom suture line is to secure the graft below the valve and not for hemostasis. Additional subannular sutures can be placed after the graft is lowered and the initial subannular sutures are tied. This will allow the additional subannular sutures to follow the natural curve of the annulus and be accurately placed through the graft, rather than be placed in a single plane, which is difficult to achieve near the left–right commissure, and places the conduction system at risk anteriorly. **B.** The horizontal mattress subannular sutures are passed from inside out through the bottom collar of the graft. The commissural stay sutures are retrieved through the graft, which is then lowered and the three subannular sutures are tied. Using pledgetted 4-0 Prolene sutures, we fix the top of the commissures, just above the valve leaflets, to the STJ of the graft. This height is appropriate for the majority of patients. This usually creates some tension on the commissures, but one should resist the temptation to locate the commissure lower, which will result in leaflet prolapse. The Prolene sutures are tied outside the graft, and the stay sutures are removed. **C.** The internal suture line approximating the annulus and sinus remnant to the inside of the graft is the next step. We begin in the left coronary sinus, using a continuous 4-0 Prolene and an RB-1 needle. Whenever possible, one should direct the needle away from the valve to minimize the chance of leaflet injury. As this is the hemostatic suture line, it should be completed meticulously and in unhurried fashion. Folds of the graft are sites of potential internal leak and bleeding and can be avoid by pulling on the aortic tag at the top of the commissure, straightening the course of the annulus and graft to facilitate sewing. We prefer to perform the internal sutures line in the order of left sinus, noncoronary sinus, and finally, the right sinus. (Reproduced with permission from Cameron DE, Vricella LA. Valve-sparing aortic root replacement with the Valsalva graft. *Op Tech Thorac Cardiovasc Surg* 2009;14:297–308. Copyright Elsevier.)

on telemetry for the duration of the hospital stay, however. The mediastinal tube is removed for outputs less than 150 mL per 24 h.

Patients with mechanical valves are started on oral warfarin on the second postoperative day. The use of daily aspirin coupled with a target International Normalized Ratio (INR) of 2.0 to 2.5 provides satisfactory anticoagulation and minimizes long-term bleeding and thrombotic events. Patients with bioprosthetic valves can be managed with aspirin alone, with no warfarin required.

The 30-day (early) mortality for aortic root replacement varies from 0 to 10 percent.[25,35] This number is approximately doubled with redo operations. Reoperation for mediastinal hemorrhage should be required in less than 10 percent of cases. Complete heart block requiring pacemaker insertion occurs in about 1 to 2 percent in most series. Stroke occurs

in approximately 1 to 4 percent of these patients. There is no practical pharmacologic strategy for the prevention of postoperative atrial fibrillation, which occurs up to one-third of the time (in patients with no previous history). Careful correction of electrolytes and chemical cardioversion with intravenous and oral amiodarone are preferred and are successful 90 to 95 percent of the time. Patients should be maintained on oral amiodarone for approximately 1 month, by which time the threat of recurrent atrial fibrillation should be resolved. In patients who require warfarin, the use of amiodarone makes it very difficult to manage the INR, and consideration should be given to alternative antiarrhythmics such as sotalol and procainamide. Patients with persistent atrial fibrillation despite attempts at chemical and electrical cardioversion should be maintained on oral warfarin until the arrhythmia resolves.

## SUMMARY

Improvements in surgical technique, modifications of the procedure, and the development of specialized graft materials have improved the outcomes of aortic root replacement significantly.

Risk factors for the development or accelerated growth of ascending AAs include aortic dissection, aneurysmal disease elsewhere in the aortic wall, smoking, renal failure, and diastolic hypertension. Ascending aortic dilatation can result from genetic conditions such as Marfan syndrome, congenital bicuspid aortic valve, and osteogenesis imperfecta as well as from excessive extracellular matrix degradation caused by unregulated activity of enzymes such as MMPs, as seen in inflammatory conditions. Aneurysmal enlargement of the aortic root can occur with an increase in the diameter of the aortic annulus (annuloaorticectasia) or without dilatation of the aortic annulus (degenerative disease).

Although certain patients may present with associated symptoms such as onset of pain from acute aortic dissection, the majority of these patients do not present with any specific physical abnormality, and many ascending AAs are detected as an incidental finding. Contrasted CT scans or MRIs, particularly those with three-dimensional reconstructions, have become the most useful diagnostic tests for evaluating the aortic root. There is no medical therapy for ascending aortic root aneurysms, and beyond therapy for blood pressure reduction and careful follow-up, including frequent radiologic imaging, surgical replacement of the aortic root is the only treatment.

For patients in whom surgical replacement of the aortic root is indicated, the surgeon must choose the appropriate ascending aortic root replacement device. Current options for aortic root replacement include composite synthetic xenograft valve-conduit prostheses and homograft replacement. Additional options include using the patient's own pulmonary valve after transposition to the aortic position (Ross procedure) and valve-sparing aortic root replacement.

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## AORTIC ROOT REPLACEMENT BOARD REVIEW QUESTIONS (CHAPTER 33)

1. Which of the following is correct regarding the modified Bentall procedure?
   A. Originally proposed by Kouchoukos
   B. Involves separate reimplantation of the coronary buttons
   C. Is the current preferred technique for aortic root replacement
   D. Prevents pseudoaneurysm developed at the coronary ostia
   E. All of the above

2. Which is correct concerning valve-sparing root replacement with the David I technique?
   A. Recreates the sinuses of Valsalva
   B. Precedes the Yacoub technique
   C. Stabilizes the aortic root with sutures placed distal to the aortic annulus
   D. Utilizes a straight tube graft
   E. The incidence of aortic insufficiency is higher than with the remodeling technique

3. Which has been shown to reduce aneurysm growth in Loeys–Dietz syndrome?
   A. Doxycycline
   B. ARB2 inhibitors
   C. β-Blockers
   D. Diuretics
   E. ACE inhibitors

4. Which dimension is correct for consideration of surgery to replace the ascending aorta?
   A. No history of connective tissue disorder—5.5 cm
   B. Marfan syndrome—5.0 cm
   C. Bicuspid aortic valve—4.5 cm
   D. Loeys–Dietz syndrome—4.0 cm
   E. All of the above

5. Which is not a common complication of the Ross procedure?
   A. Bleeding
   B. Injury to the first septal perforator
   C. Heart block
   D. Dilation of the autograft
   E. Thrombosis of the pulmonary homograft

## ANSWERS

1. **Answer: E.** The current preferred technique for aortic root replacement is the modified Bentall procedure, which requires reimplantation of the coronary arteries. This modification was proposed by Kouchoukos as a solution to the problem of coronary ostia pseudoaneurysm that occurred after other operations.
2. **Answer: D.** The David I operation uses a straight tube graft and does not recreate the sinuses of Valsalva. It was introduced after the Yacoub remodeling technique and stabilizes the root with sutures placed proximal to the aortic annulus. The incidence of aortic insufficiency is lower when compared to the remodeling technique.
3. **Answer: B.** Losartan has been shown to slow growth of aneurysms associated with Loeys–Dietz syndrome.
4. **Answer: E.** These are the generally accepted dimensions for surgical intervention for aneurysm of the ascending aorta.
5. **Answer:** E. Stenosis and/or insufficiency occurs in the pulmonary homograft in up to 20 percent of patients, but thrombosis is rare. The combined use of the autologous pulmonary valve and the homograft pulmonary valve is suitable for young, active patients that desire to avoid anticoagulation.

# 34 Mitral Valve Pathophysiology

*Tomasz A. Timek*
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**KEY CONCEPTS**

- The normal mitral valve annulus is a saddle-shaped structure with 3:4 ratio of the anterior–posterior to commissure–commissure distance.
- Mitral stenosis is usually a result of rheumatic fever, and valvular pathology represents antigen cross-reactivity from Group A streptococcus resulting in valvulitis, myocarditis, or pancarditis.
- Fibroelastic deficiency and Barlow disease are the predominant forms of degenerative mitral valve disease leading to mitral regurgitation. Fibroelastic deficiency is found in older patients whereas congenitally excessive valve tissue seen in younger patients is observed with Barlow valve.
- Chordal rupture is the most common etiology of mitral regurgitation in degenerative mitral valve disease.
- Ischemic mitral regurgitation (IMR) is associated with a localized left ventricular infarct with subsequent chamber remodeling and perturbation in the subvalvular apparatus. Functional mitral regurgitation (FMR) is associated with end-stage dilated cardiomyopathy.
- Both FMR and IMR are characterized by subvalvular remodeling and annular dilation.
- Leaflet remodeling may contribute to the pathophysiology and severity of both IMR and FMR.
- Annular dilation and perturbed leaflet coaptation tend to be symmetric in FMR and asymmetric in IMR.

## ANATOMY

The mitral valve comprises two leaflets with the anterior leaflet being larger and sail-like traversing approximately one-third of the annular circumference. The posterior leaflet is smaller, more rectangular-shaped, and typically has three scallops denoted as P1, P2, and P3 from the anterolateral toward the posteromedial commissure. Corresponding coapting regions of the anterior leaflet are labeled as A1, A2, and A3 according to the Carpentier nomenclature, although no anatomic landmarks, such as distinct interscallop clefts found in the posterior leaflet, separating these regions exist (Fig. 34-1). The free edge of the leaflets is called the bare or membranous zone, with the remainder of the leaflets termed the rough zone. The histologic structure of the leaflets includes the fibrosa, a solid collagenous core that is continuous with the chordae tendineae, and the spongiosa that consists of few collagen fibers but abundant proteoglycans, elastin, and mixed connective tissue cells, which is on the atrial surface and forms the leaflet leading edge. On the atrial aspect of both leaflets, this surface (the atrialis) is rich in elastin whereas the ventricular side (the ventricularis) is much thicker, is confined mostly to the anterior leaflet, and is densely packed with elastin. Nutrients to leaflet tissue are supplied by annular and ascending chordal vessels. The leaflets have long been thought to be passive, inert structures at the hemodynamic mercy of the ebb and flow of ventricular contraction, but recent data refute this view. Leaflet tissue is richly innervated, has intrinsic contractile properties, complex heterogeneous ultrastructure, and may be important in modulating timely and efficient valve closure.[1,2]

The mitral annulus is a less well-defined structure (particularly the posterior component) without a clear "ring" configuration that anchors the base of the leaflets. It has two major fibrous components, termed the trigones. The right fibrous trigone is part of the central fibrous body of the heart, being in continuity with the aortic valve, the tricuspid valve, and the membranous septum. The portion of the annulus that anchors the anterior mitral leaflet is in direct continuity with portions of the left and noncoronary aortic

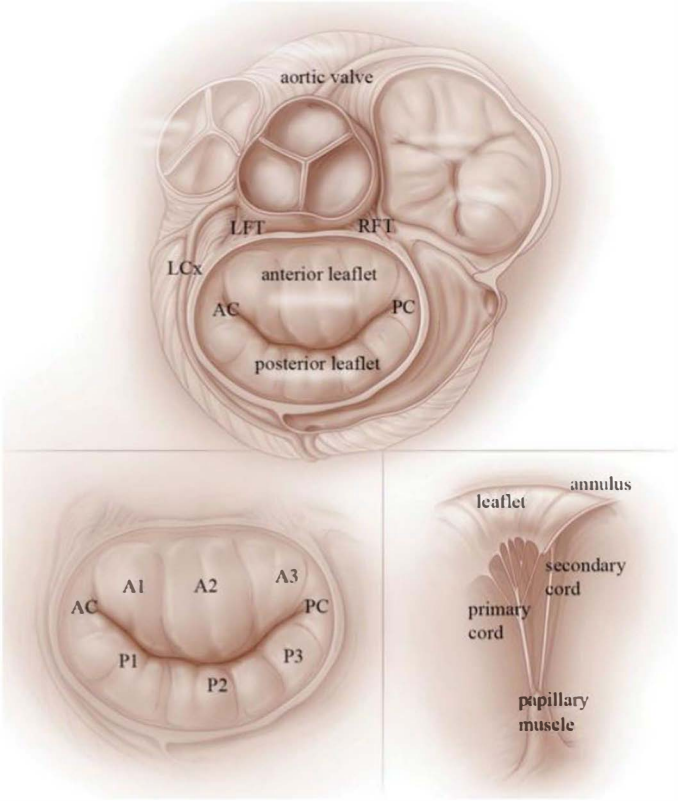



**FIGURE 34-1** Anatomy of the mitral valve complex. LCx, left circumflex coronary artery; RFT, right fibrous trigone; LFT, left fibrous trigone; AC, anterior commissure; PC, posterior commissure.

valve leaflets. The intertrigonal distance defines the fibrous or anterior portion of the mitral annulus and, like the height of the anterior mitral leaflet, is an important clinical marker for surgical annuloplasty sizing as the fibrous annulus has been thought to remain unchanged across the spectrum of mitral disease; however, this region may remodel in ischemic mitral regurgitation (IMR) and functional mitral regurgitation (FMR). The posterior, or lateral, annulus is mostly muscular and manifests most of the dynamic shape and area change of the mitral opening during the cardiac cycle. The normal mitral valve area ranges between 4 and 6 $cm^2$ whereas the normal annular diameter ranges between 5 and 11 $cm^2$ and maintains a 3:4 ratio of the anterior–posterior to the commissure–commissure distance. The annulus has a saddle-shaped configuration with the highest points located anteriorly and posteriorly and the lowest points located at the commissures. This three-dimensional annular structure may be important for proper leaflet stress distribution and effective valve closure. The annulus increases in size during early diastole and decreases rapidly during late diastole and early systole with most of size reduction achieved before ventricular contraction.[3] It becomes less planar during systole as the anterior portion of the "saddle" becomes more accentuated simultaneously optimizing mitral valve closure and left ventricular (LV) outflow tract size during the period of ejection. In addition, the mitral annulus descends toward the LV apex during systole; the duration, average rate, and magnitude of annular displacement correlate with the rate of left atrial filling and emptying.

There are two major papillary muscles that support the mitral valve. Both papillary muscles provide chordae tendinae to both mitral leaflets. The anterolateral papillary muscle usually has one major head and is larger; the posteromedial papillary muscle is flatter and can have two or more heads. Vascular supply to the anterolateral papillary muscle is usually from both the left anterior descending and the circumflex arteries, while the posteromedial papillary muscle is often supplied only by the posterior descending artery. First-order chordae, designed to prevent leaflet prolapse, arise near the tips of the papillary muscles and insert into the leading edge of the leaflets while second-order chordae insert farther back into the leaflet, either on the rough zone or at the junction between the rough zone and the clear zone. These chordae are larger and thicker and serve to stabilize the valve, maintain valvular–ventricular continuity, and aid ventricular systolic performance. Third-order chordae arise from ventricular wall trabeculations and insert near the annulus. The chordae also serve as scaffolding for nutrient vessels to supply leaflet tissue while their ultrastructural composition is related to their function.[4]

## MITRAL STENOSIS

Mitral valve stenosis is usually the result of rheumatic fever suffered in childhood or early adulthood. A definite history of rheumatic fever can be obtained in only about 50 to 60 percent of patients; women are affected more often than men by a 2:1 to 3:1 ratio.[5] Nearly always acquired before age 20, rheumatic valvular disease becomes clinically evident one to three decades later. Rheumatic disease remains a significant problem throughout the world, although its incidence has fallen sharply in industrialized countries. Rheumatic heart disease is a result of antigen cross-reactivity from group A β-hemolytic *Streptococcus* culminating in pancarditis, affecting valve leaflets, endocardium, and myocardium to varying degrees. Mimicry between streptococcal antigens and cardiac tissue proteins, combined with high inflammatory cytokine and low interleukin-4 production, leads to the development of autoimmune reactions and cardiac tissue damage.[6] Mitral valve involvement is the most common, followed by combined mitral and aortic involvement. Commissural fusion, chordal fusion and shortening, and leaflet fibrosis and retraction as well as significant calcifications are most commonly seen in rheumatic mitral valve disease. Grossly, the mitral opening takes on the classically described "fish mouth" appearance (Fig. 34-2).

Physiologically, mitral stenosis elevates the transvalvular gradient during diastole between the left atrium and the left ventricle, leading to restricted ventricular filling and increased left atrial pressure. Mean valve area of less than 1.0 $cm^2$ and a mean transvalvular gradient greater than 10 mm Hg is considered to be severe mitral stenosis. The transvalvular pressure gradient is a function of the square of the transvalvular flow rate; thus, high transvalvular gradient may be associated with a normal cardiac output, but if cardiac output is low, only a modest transvalvular gradient may be present. In addition, mitral transvalvular flow depends on cardiac output and heart rate. An increase in heart rate decreases the duration of LV filling during diastole and consequently increases the mean transvalvular gradient and left atrial pressure. The dynamic nature of the transvalvular gradient may therefore become significant and hence cause symptoms only with exercise; however, chronic and progressive valvular stenoses are usually accompanied by elevated left atrial pressures and increased pulmonary vascular resistance and pulmonary hypertension. Maintenance of sinus rhythm becomes paramount as atrial contraction augments flow through the stenotic valve, thereby helping to sustain adequate forward cardiac output. However, the dilated atrium becomes substrate for development of atrial fibrillation, which significantly limits ventricular filling. The development of atrial fibrillation decreases cardiac output by 20 percent or more; atrial fibrillation with a rapid ventricular response can lead to acute dyspnea and pulmonary edema. Major determinants of atrial fibrillation in patients with rheumatic heart disease include older age and larger LA diameter.[7] The risk of intra-atrial thrombus from stagnant flow within the enlarged chamber increases concurrently.



**FIGURE 34-2** Autopsy specimen of mitral stenosis. Heavy calcification of the both mitral leaflets with classic "fish mouth" shape of the stenotic mitral orifice.

Isolated mitral stenosis is associated with LV chamber size that is normal or smaller than normal with typically low end-diastolic pressure. Cardiac output is diminished due to underfilling of the ventricle from inflow obstruction rather than LV myocardial dysfunction. During exercise, LV ejection fraction may increase, but this response is blunted by the shorter diastolic filling periods at higher heart rates; therefore, stroke volume and cardiac output do not increase proportionally to physiologic demand. In approximately 25 to 50 percent of patients with severe mitral stenosis, LV systolic dysfunction is present as a consequence of associated problems (e.g., mitral regurgitation, aortic valve disease, ischemic heart disease, rheumatic myocarditis or pancarditis, and myocardial fibrosis), and in these patients, LV end-systolic and end-diastolic volumes may be larger than normal. In severe chronic mitral stenosis with elevated pulmonary vascular resistance, pulmonary arterial pressure is elevated at rest and can approach systemic pressure with exercise. A pulmonary arterial systolic pressure greater than 60 mm Hg significantly increases impedance to right ventricular emptying and produces high right ventricular end-diastolic and right atrial pressures as well as eventual tricuspid insufficiency.[8] In time, right ventricular systolic performance deteriorates.

## MITRAL REGURGITATION

Structural changes of the mitral valve may produce valvular insufficiency by adversely impacting one or more components of the mitral valve complex: mitral annulus, mitral leaflets, chordae tendinae, or LV geometry. Carpentier classified mitral regurgitation into three main pathoanatomic types based on the leaflet motion: normal leaflet motion (type I), leaflet prolapse or excessive motion (type II), and restricted leaflet motion (type III).[9] Type III is further subdivided into types IIIa and IIIb based on leaflet restriction during

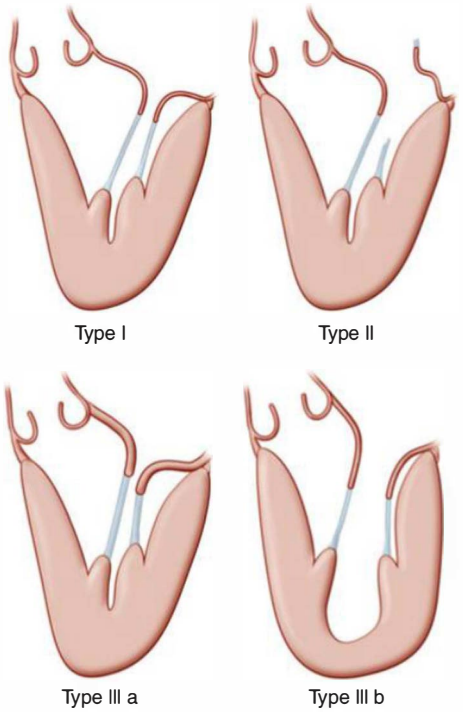



FIGURE 34-3 Schematic representation of Carpentier classification of mitral leaflet motion.

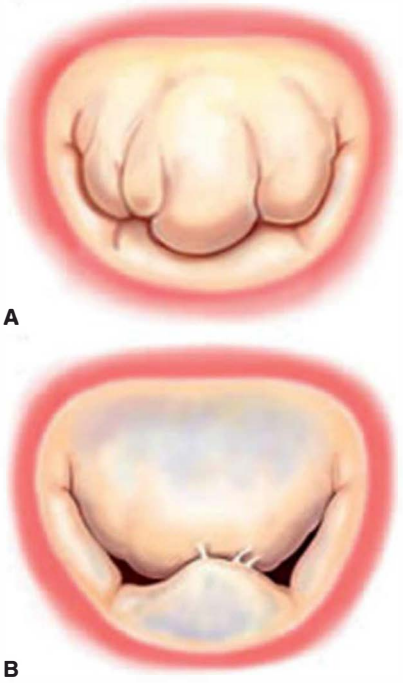



FIGURE 34-4 Degenerative mitral valve disease. **A**. Barlow disease with anterior leaflet prolapse. **B**. Fibroelastic deficiency with ruptured chordae to P2 segment of the posterior leaflet.

diastole (type IIIa) or during systole (type IIIb) (Fig. 34-3). Mitral regurgitation with normal leaflet motion can be the result of annular dilatation usually due to LV remodeling. Leaflet prolapse typically results from a floppy mitral valve with chordal elongation and/or rupture, but rarely can also be seen in patients with coronary artery disease who have papillary muscle elongation or rupture. Mitral regurgitation due to restricted leaflet motion is associated with rheumatic valve disease (types IIIa and IIIb), ischemic heart disease (IMR with type IIIb restricted systolic leaflet motion secondary to apical tethering or tenting), and dilated cardiomyopathy (type IIIb). This elegant classification system allows for standardized nomenclature while reflecting the underlying pathophysiology of mitral insufficiency across a wide spectrum of structural deformities of the mitral valve complex.

## Degenerative Mitral Regurgitation

Degenerative mitral valve disease is a major cause of mitral insufficiency requiring surgical evaluation in the United States. Included in this category are myxomatous degeneration, floppy mitral valve, and mitral valve prolapse. The etiology of mitral valve prolapse is both acquired (*fibroelastic deficiency* in older patients) and congenital or heritable, with excess spongy, weak fibroelastic connective tissue constituting the leaflets and chordae tendineae (*Barlow valve*, in younger patients) (Fig. 34-4). Mitral valve prolapse is most common in young women and can have a familial component; the more severe forms of insufficiency are more common in men.

In myxomatous disease, the mitral leaflets become thickened and opaque and the degenerative process may extend down the chordae and out onto the annulus. Histologically, elastic fiber and collagen fragmentation and disorganization are present, and acid mucopolysaccharide material accumulates in the leaflets.[10] Myxomatous degeneration commonly involves the annulus, resulting in annular thickening and dilatation. All these changes are pronounced in young patients with Barlow valves but can be minimal in older subjects with fibroelastic deficiency, in whom the noninvolved posterior leaflet scallops and anterior leaflet are normal and thin. A minority of patients (5–10 percent) with mitral valve prolapse progress to symptomatic mitral insufficiency; these patients can be placed into three categories: isolated chordal rupture, isolated annular dilatation, and combined chordal rupture and annular dilatation (most common). Chordal rupture can result in acute mitral insufficiency and should be suspected in patients with no previous clinical history of coronary artery disease or acute myocardial infarction. Chordal rupture is typically found in older patients with prolapse due to fibroelastic degeneration without much accompanying leaflet pathology. Posterior chordal rupture, usually subtending just the middle scallop, is

the most frequent finding, followed by anterior chordal rupture and then combined anterior and posterior chordal rupture.

## Functional and Ischemic Mitral Regurgitation

FMR is the result of incomplete mitral leaflet coaptation in the setting of LV dysfunction and dilatation with or without annular dilatation (e.g., dilated cardiomyopathy or ischemic cardiomyopathy). IMR, a subset of FMR, is usually associated with a localized LV insult due to myocardial infarction with subsequent remodeling and geometric perturbations in the subvalvular apparatus. Historically, FMR and IMR occur in the setting of what has been thought as structurally normal mitral valve leaflets and are thus considered "functional." These clinical entities frequently complicate myocardial infarction and carry a poor prognosis in the setting of both coronary disease and idiopathic dilated cardiomyopathy.

"Functional mitral regurgitation" has been used interchangeably to refer to mitral insufficiency due to end-stage ischemic dilated cardiomyopathy and that due to idiopathic dilated cardiomyopathy, yet the mechanisms of mitral regurgitation in these clinical conditions differ significantly.[11] The lack of standardized application of "functional" and "ischemic" etiologies of mitral insufficiency represents a considerable hindrance in the appropriate interpretation and comparison of clinical studies, especially since coronary artery disease and LV dysfunction can span a wide range of clinical presentations. Despite these limitations, many investigators today use "functional" to refer to mitral regurgitation in the setting of severe LV dysfunction and dilation usually defined by an ejection fraction of less that 30 percent regardless of etiology.[12] IMR, in contrast, refers to patients with coronary artery disease and mitral regurgitation with lesser degree of LV dilation, more preserved ventricular function, and more asymmetric ventricular remodeling usually affecting the posterolateral ventricular wall.[13] Not surprisingly, these entities lie on a clinical continuum and cannot always be precisely defined due to the heterogeneity of ischemic heart disease. Animal models of both local and global LV systolic dysfunction and remodeling associated with mitral regurgitation have been developed and permit identification of the contributing geometric factors that result in FMR and IMR in controlled settings.[14,15]

IMR encompasses a difficult patient population that is characterized by high operative mortality, poor long-term outcomes, and frequent recurrent regurgitation after standard surgical repair.[16] Optimal surgical repair and improved clinical outcomes can only be achieved with better knowledge of the pathophysiology of IMR, which is currently incompletely understood. Clinical studies estimate the incidence of postinfarction mitral regurgitation detected on echocardiography to be approximately 20 percent with up to 12 percent of patients having moderate or severe regurgitation.[17,18] In patients who progress to clinically symptomatic heart failure, the incidence of mitral regurgitation reaches 56 percent with approximately 16 percent having moderate or severe regurgitation.[19] By these estimates, approximately 860,000 patients have clinically significant IMR (moderate-to-severe grade) in the United States with the prevalence bound to increase with the aging population and new therapies to improve postinfarct survival. Echocardiographic studies have shown that mitral regurgitation is an independent predictor of heart failure and death in infarct survivors beyond 30 days. The degree of mitral regurgitation shows a graded relation to 1-year postinfarct mortality, and even mild degree of IMR has been shown to have prognostic significance. Similarly, the presence of mitral regurgitation in dilated cardiomyopathy (or FMR) portends a poor prognosis and is associated with high cardiovascular morbidity and mortality in both ischemic and idiopathic etiologies.

The causative mechanism of IMR appears to lie in the annular and ventricular levels rather than leaflet or chordal structure leading to such labels as "ischemic," "functional," and "nonorganic" being clinically applied. Although IMR is a prevailing clinical entity, it has not been consistently defined in the literature adding to considerable confusion and conflicting results. Rankin and colleagues defined IMR as "valvular insufficiency arising from coronary disease without primary leaflet or chordal pathology."[20] Yet this definition appears overly broad as the spectrum of coronary disease and LV dysfunction varies tremendously in IMR ranging from preserved ventricular function to moderate dysfunction to end-stage dilated ischemic and idiopathic cardiomyopathy. A useful definition of IMR was suggested by Replogle who subclassified patients in this group into three entities: (1) sudden-onset mitral regurgitation due to acute myocardial infarction and papillary muscle rupture and/or LV wall dysfunction, (2) mitral regurgitation associated with coronary artery disease with normal mitral leaflets, and (3) mitral regurgitation caused by end-stage ischemic dilated cardiomyopathy.[21] The first of these three etiologies usually represents a catastrophic event with very high mortality but fortunately low incidence. Thus, it is the latter two types of IMR that represent the bulk of the clinical disease.

### LEFT VENTRICULAR GEOMETRY

Mitral regurgitation, whether functional or ischemic in origin, is usually associated with LV dilation; however, the degree of chamber remodeling may differ significantly. In a canine model of dilated cardiomyopathy induced with coronary microembolization, Kono and colleagues found increased LV sphericity, or ventricular globularization, to be closely associated with FMR.[22] Echocardiographic studies in patients with nonischemic dilated cardiomyopathy confirm LV diameter and sphericity to be major predictors of mitral regurgitation; sphericity has also been shown to accompany progression of mitral regurgitation in end-stage ischemic heart disease and recurrent regurgitation after ventricular reduction surgery.[23] IMR, on the other hand, appears not to be solely dependent on global LV dilation but rather on a localized LV insult.[24] Nonetheless, recurrent regurgitation after ring annuloplasty for IMR is associated

with a persistently spherical ventricle underscoring the spectrum of clinical disease and blurring of boundaries between IMR and FMR as LV dysfunction and dilation progress. Experimentally in an ovine model, a small posterior infarct increases cavity size by 48 percent, yet results in no mitral regurgitation after 8 weeks, whereas large infarcts with lesser degree of LV dilation result in immediate severe regurgitation.[25] In a chronic model of ovine posterolateral ischemia, the end-systolic volumes did not differ between animals that did or did not develop significant mitral regurgitation.[24]

Clinically, IMR is thought to be more frequent with inferior than anterior myocardial infarct; however, equal incidence or greater association with anterior infarct has also been reported.[26–28] In an animal model, both large and moderate infarcts of the anterior wall have not been associated with mitral regurgitation even with LV enlargement of 150 percent.[25] These experimental models, however, represent isolated regional ischemia with unaffected remote territory; this scenario does not reflect most clinical settings as the majority of patients with IMR suffer from multivessel coronary artery disease. It is this heterogeneity of human disease that does not permit identification of clear boundaries in the pathogenesis of infarct-specific mitral regurgitation. In the clinical setting, IMR associated with anterior wall infarct is usually accompanied by greater LV and mitral annular dilation, more impressive annular flattening, and substantially reduced ejection fraction compared with findings with inferior infarct.[29,30] Anterior infarct may not sufficiently affect critical annular–subvalvular spatial relationships that are perturbed by a smaller posterolateral infarct, yet with chronic remodeling and deterioration in LV function, IMR does result. Thus, IMR associated with anterior infarct may lie closer on the clinical spectrum to FMR characterized by severely depressed LV function, global LV dilation, and annular enlargement. In contrast, inferior infarct is associated with less global LV dilation and dysfunction but more substantial perturbation of the mitral valve apparatus. Experimentally, surgical interventions used to correct chronic IMR have not been shown to be associated with altered LV size. However, reverse remodeling after restrictive annuloplasty is more predictable in patients with smaller LV size (end-diastolic volume less than 65 mm), and patient survival is superior.

## MITRAL ANNULUS

The mitral annulus is a nonplanar structure in shape of a saddle with significant elevation of the midseptal annulus (also known as the annular "saddle horn"). The three-dimensional shape of the annulus, conserved across mammalian species, may be important for proper leaflet stress distribution. The annulus subsequently flattens with onset of FMR and IMR in both clinical and experimental studies. Progressive and heterogeneous flattening of the annulus was well documented in a chronic study of ovine IMR (Fig. 34-5).[31] Although annular flattening may not be directly related to the pathogenesis of IMR, altered annular shape may act to increase leaflet forces and lead to pathologic remodeling that, in the chronic state, could contribute to the evolution of mitral regurgitation. Naturally, abnormal annular geometry has surgical implication in terms of design and implantation of annular prostheses.

In patients with nonischemic cardiomyopathy and depressed ejection fraction of 25 percent, annular size was the chief determinant of mitral regurgitation.[32] Mitral regurgitation associated with annular dilation may be present in patients with depressed LV function and ventricular remodeling; the degree of annular dilation, especially in the septal–lateral dimension, correlates with the degree of LV systolic dysfunction in patients with dilated cardiomyopathy. Annular dilation and reduced transmitral pressure were found to be responsible for mitral regurgitation in a group of patients with a mean EF of 23 percent, while annular enlargement and ejection fraction were observed to be the strongest predictors of leaflet tenting area in a similar patient population.[33] Experimentally in the canine model of tachycardia-induced cardiomyopathy, mitral regurgitation was predicted

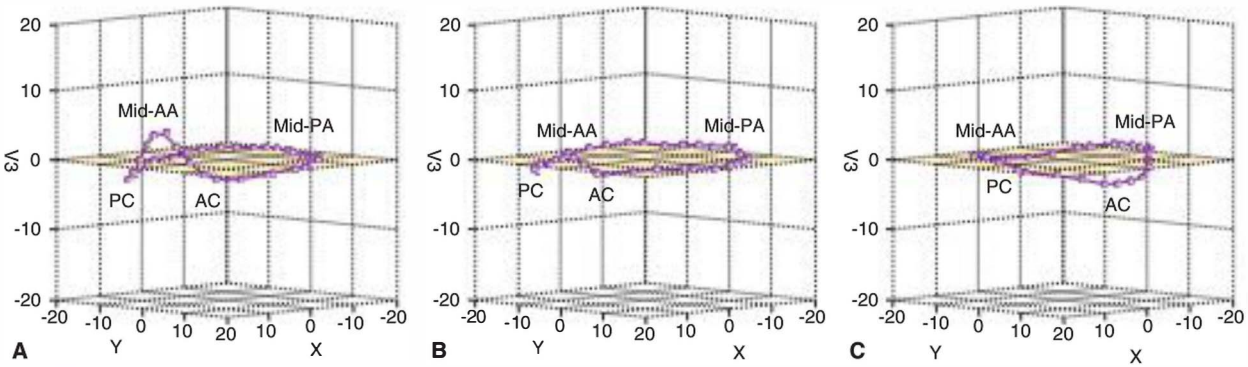



**FIGURE 34-5** The three-dimensional geometry of a single ovine mitral annulus shown **A** at baseline, **B** 1 h after myocardial infarction, and **C** 8 weeks after myocardial infarction. Progressive flattening of the mitral annular three-dimensional structure is observed across time. The positions of the midanterior annulus (Mid-AA), the midposterior annulus (Mid-PA), the anterior commissure (AC), and the posterior commissure (PC) are indicated. (Reproduced from Ryan JB, et al. *Ann Thorac Surg* 2007;84(2):553–559.)

purely by the degree of annular dilation; device-driven increase in annular circumference by 25 percent was found to produce severe mitral regurgitation in healthy dogs.[34] In an *in vitro* porcine valve model, isolated annular enlargement from 6.8 to 12 $cm^2$ increased regurgitant volume from less than 3 to 18.5 mL; in another study, an annular area increase of 1.75 times baseline led to significant increase in mitral regurgitation.[35] In addition, finite element analysis showed that an isolated increase in annular circumference is associated with incomplete leaflet coaptation throughout systole without displacement of the coaptation point. These findings support the notion that mitral regurgitation in end-stage dilated cardiomyopathy is chiefly related to substantial annular dilatation, particularly in the septal–lateral dimension.

In an acute model of IMR provoked by a localized LV insult, annular dilation was a component of the geometric perturbation leading to mitral regurgitation but not the sole etiology.[36] Similar findings have been found by other investigators in both acute and chronic experimental IMR, although acute posterior leaflet interscallop insufficiency may be related to annular dilation alone. These findings are corroborated by clinical studies that identify annular dilation as a contributor to the development of mitral regurgitation; however, subvalvular deformations play the central role. Furthermore, in clinical echocardiographic studies, the pattern of annular dilation in IMR is more asymmetric whereas annular dilation associated with FMR was diffuse and symmetric. With both FMR and IMR, annular perimeters increase (including the septal portion) with bulk of annular dilation along the lateral annulus.[37] Previous studies have shown that the lateral annulus is more susceptible to dilation during acute ischemia, and patients with IMR exhibit decreased motion of the lateral annulus during the cardiac cycle. The lateral annulus undergoes not only substantial dilation but also a decrease in its "sphincteric" action, which reduces mitral annular area during the cardiac cycle. This reduction may be due to decreased LV systolic function as annular contraction is augmented with increased inotropy. Clinically, decreased annular contraction occurs in patients with ischemic and dilated cardiomyopathy and is a predictor of mitral regurgitation.[38] During cardiac resynchronization therapy, resynchronizing annular segments leading to more effective annular contraction is associated with reduced mitral regurgitation in patients with congestive heart failure and left bundle branch block. It is reasonable to conjecture that dysfunctional annular sphincteric mechanism contributes to both FMR and IMR.

## PAPILLARY MUSCLES

Papillary muscle displacement has been identified as a key component in the pathogenesis of IMR; however, isolated papillary muscle dysfunction does not lead to significant mitral regurgitation, and dysfunction of the underlying LV wall is needed to induce clinically important regurgitation.[39] Specifically, systolic dysfunction of the posterior/inferior LV wall inclusive of the posterior papillary muscle with subsequent leaflet tethering appears to be the prerequisite lesion for the evolution of experimental and clinical IMR. Infarction of the anterior wall and the anterior papillary muscle does not result in mitral regurgitation until advanced LV dilation and systolic dysfunction develop. In patients with very low ejection fractions and remarkable LV dilation, synchronization of LV contraction at papillary muscle insertion sites can, however, reduce the degree of mitral regurgitation. Posterior papillary muscle dysfunction has been shown to reduce the severity of mitral regurgitation through effective ischemic "elongation" of the papillary muscles that ameliorates apical leaflet displacement in acute ovine IMR[40] and in patients as the adjacent LV wall remodels. Experimentally, plication of a posterolateral infarct can reduce the degree of IMR through papillary muscle repositioning, thereby underscoring the importance of local subvalvular geometric perturbations associated with IMR. Gorman and colleagues reported apical displacement of the anterior papillary muscle tip and basilar dislocation of the posterior papillary muscle tip in acute ovine IMR; based on papillary muscle position, they postulated that IMR in this model could be associated with leaflet prolapse near the posterior commissure and restriction near the anterior commissure.[41] Accordingly, Nielsen and colleagues observed decreased tension in the chordae emanating from the ischemic posterior papillary muscle but increased tension in those arising from the normally contracting anterior papillary muscle in a porcine model of acute IMR.[42] Such leaflet configuration due to asymmetric papillary muscle dislocation has also been suggested by *in vitro* modeling.

In experimental FMR, anterior and posterior papillary muscle displacement, assessed by the distance from each papillary muscle tip to the midseptal annulus, was almost identical consistent with the symmetric global LV dilation associated with cardiomyopathy. This finding is in contrast to a localized ischemic insult seen in the IMR, where posterior papillary muscle tethering was almost twice as great as that of the anterior papillary muscle. No apical displacement of either papillary muscle tip was observed, but there was impressive increase in the interpapillary distance that has been identified as a marker of LV dilation and predictor of FMR. Also, greater global LV dysfunction and remodeling have been associated with symmetric papillary muscle tethering.

## MITRAL LEAFLETS

Experimental and clinical research has focused primarily on altered annular and subvalvular geometry as the cause of FMR and IMR, while valvular leaflet tissue properties have been thought to be essentially unchanged. However, human studies reveal that both anterior and posterior mitral leaflets remodel in cardiomyopathy, suggesting that leaflet tissue is a contributor to the pathophysiology of FMR. Anatomic and biochemical studies of the mitral valve leaflets have shown normal valvular tissue to be richly innervated and having a complex blood supply, heterogeneous biochemical composition, and nonhomogeneous deformation.[43,44] Recent observations have demonstrated that mitral leaflets from human transplant recipient hearts with FMR have a much different

biochemical profile than control leaflets, having significantly higher DNA content and collagen concentration with greatest deposition in the anterior leaflet free edge.[45] Overall, human heart failure leaflets were 28 to 41 percent longer than control values. Further mechanical analysis revealed that the leaflet tissue was 61 percent stiffer in the radial direction and 50 percent stiffer in the circumferential direction than control leaflets reflecting microstructural alterations. These data suggest prominent biochemical and ultrastructural remodeling of leaflet tissue particularly in the region of the free edge. The anterior leaflet edge and the entire posterior leaflet have been found to have a relatively thin collagenous layer, and these regions may be particularly prone to greater remodeling as annular dilation increases leaflet stresses, and collagen synthesis is upregulated in response. Greater remodeling in the coaptation region of the leaflets may not be surprising given the nonhomogeneous deformation of the anterior leaflet in an *ex vivo* porcine leaflet model.[46] The anterior leaflet in normal porcine valves stretches significantly after valve closure along a radial gradient from the mitral annulus to the leaflet edge. In the ovine FMR model, the greatest anterior leaflet remodeling occurs in the area of maximum deformation, that is, the leaflet-leading edge or free margin.[47] Mitral leaflets, therefore, are not inert flaps strictly bound to the hemodynamic conditions of the left ventricle but rather active components of the valvular–ventricular complex capable of regulating valvular function in health and disease.

Recently, Tibayan and colleagues found significantly increased radii of curvature of both leaflets at 7 weeks after posterolateral infarct in an ovine model.[48] This finding, due to stretching of the leaflets from papillary muscle displacement leading to flattening of leaflet geometry, is consistent with the fact that altered leaflet geometry with concave shape of the leaflets relative to the left atrium is a strong predictor of IMR in the clinical setting.[49] Septal–lateral annular dilation and altered papillary muscle position emerged as predictors of anterior leaflet shape in an animal model[48]; clinically, leaflet length correlated with annular diameter in human transplant recipient hearts.[45] Annular dilation along with subvalvular changes can be expected to stretch leaflet tissue across the valve orifice and alter loading conditions, thus leading to leaflet remodeling as a compensatory mechanism that becomes exhausted as ventricular and annular pathologic changes progress. Such leaflet stretching coupled with annular flattening can be expected in increased stresses on the leaflet and thus induce tissue remodeling as seen in the chronic model of IMR. The possible effects of altered valvular mechanical forces, tissue properties, and biochemical composition associated with FMR and IMR on leaflet remodeling are summarized in Figure 34-6. Recent

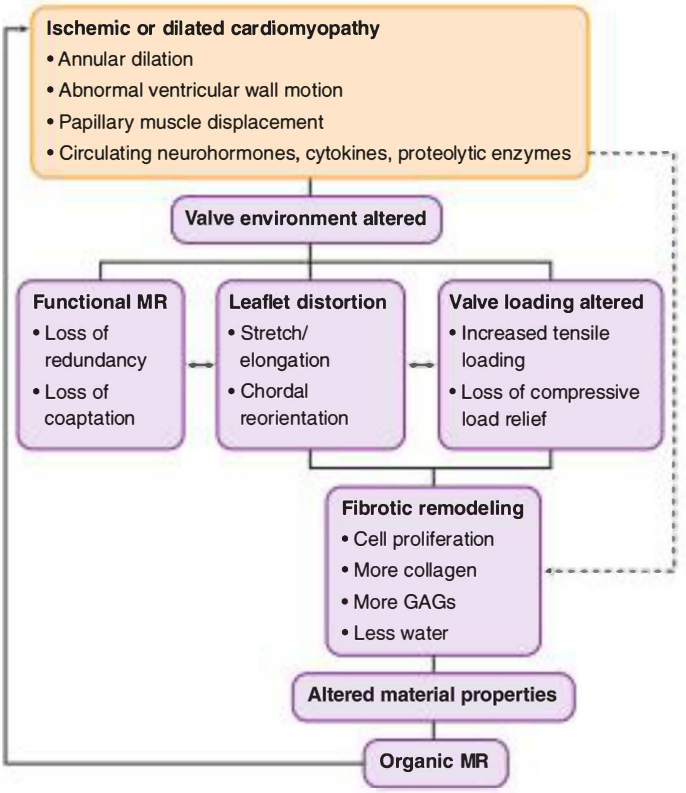



**FIGURE 34-6** Proposed mechanisms for valvular remodeling in IMR and FMR from altered mechanical loads, tissue properties, and biochemical composition of the mitral leaflets. (Reproduced from Grande-Allen KJ, et al. *J Am Coll Cardiol* 2005;45:54–61.)

echocardiographic findings in patients with reduced LV function and previous infarct demonstrated leaflet area enlargement in patients with and without mitral regurgitation, but significant regurgitation was associated only with inadequate leaflet remodeling relative to the demands of subvalvular tethering geometry.[50] Therefore, heterogeneity of leaflet remodeling may partially contribute to the wide spectrum of mitral regurgitation seen clinically. Furthermore, it is conceivable that in the evolution of mitral regurgitation, leaflet motion changes from restriction to normal leaflet motion with progressive chamber dilation and leaflet tissue remodeling, and IMR and FMR represent two points on a clinical continuum.

## LEAFLET COAPTATION

In FMR and IMR, disruption of normal leaflet coaptation is the final common pathway of annular and subvalvular geometric perturbations. It is this coupling that translates the "ventricular" disease of FMR and IMR into a valvular problem of mitral regurgitation. Apical leaflet displacement associated with LV dysfunction was first described as incomplete mitral valve closure and has subsequently been referred to as "leaflet tenting."[51] Since these pioneering efforts, multiple experimental and clinical studies have focused on coaptation depth, also referred to as coaptation height, and leaflet tenting area as representing the sum of geometric deformations leading to mitral regurgitation. These parameters are easily measured with echocardiography or magnetic resonance imaging and lend themselves to quantification (Fig. 34-7). However, IMR can be associated with normal, tethered, or prolapsed leaflet motion with symmetric or asymmetric leaflet deformity. Therefore, increases in tenting area may be due to leaflet tethering, annular dilation, or both.

In experimental FMR, leaflet motion was found to be normal without evidence of restriction or tethering. Therefore, leaflet edges were simply displaced along the main direction of annular enlargement, the septal–lateral diameter, and leaflet occlusion area was exhausted with progressive annular dilation resulting in increased leaflet edge separation.[47] Similar findings were noted echocardiographically in human subjects with dilated cardiomyopathy.[52] Tenting area was larger in patients with FMR secondary to significant annular dilatation, yet coaptation depth also increased; this finding was also thought to be secondary to annular dilation as papillary muscle tethering and chordal length did not change. Although annular dilation may affect coaptation depth if subvalvular geometry remains constant, it is septal–lateral annular enlargement that exhausts mitral leaflet redundancy resulting in mitral regurgitation by decreasing leaflet coaptation length (i.e., the length of leaflet apposition at the coaptation line).

Tethering of both leaflets has also been observed echocardiographically in patients with IMR. Symmetrical leaflet deformation occurred in patients with idiopathic dilated cardiomyopathy, whereas asymmetric leaflet geometry was observed in those with an ischemic etiology, yet all patients showed increased coaptation depth indicative of tethering.[53] Similarly, in patients with mitral regurgitation and prior anterior myocardial infarct, the leaflets were widely tethered

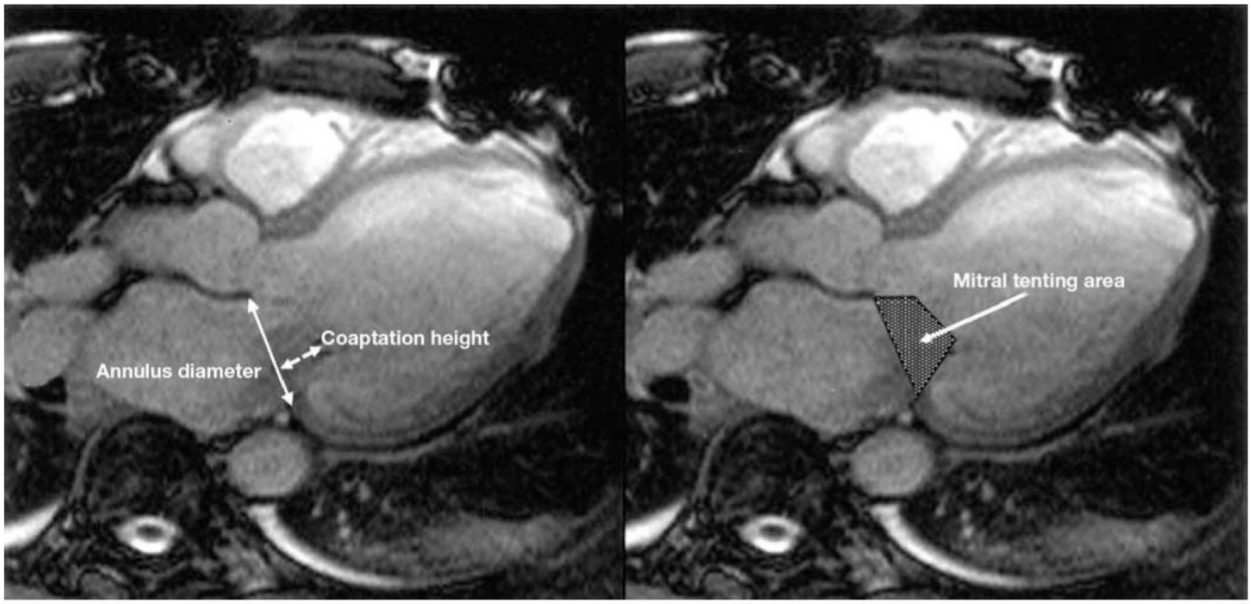



**FIGURE 34-7** Cine magnetic resonance imaging three-chamber view of a patient's heart demonstrating the measurement of annulus diameter and coaptation height (left), and mitral tenting area (right) of the mitral valve. Similar measurements can be derived echocardiographically. (Reproduced from Srichai MB, et al. *Ann Thorac Surg* 2005;80:170–178.)

toward the ventricle, whereas in the setting of inferior infarct, the tethering was more localized and tenting volume reduced. Indeed, leaflet deformation in patients with anterior infarct, characterized by more significant LV dysfunction and dilation, resembles more of the findings observed in idiopathic dilated cardiomyopathy than in localized inferior infarct with preserved LV function. Patients with IMR have significantly increased coaptation depth indicative of tethering compared with those with idiopathic dilated cardiomyopathy and global LV dilation, an entity that is often associated with substantial annular dilation. Valvular tenting and decreased annular contraction are two clinical predictors of effective regurgitant orifice, thereby underscoring the importance of annular enlargement and leaflet tethering in the genesis of mitral regurgitation. This additive effect impacting leaflet coaptation has been demonstrated in a chronic model of IMR[24] (Fig. 34-8). In addition, IMR may not only be a result of dysfunctional leaflet coaptation, but also due to posterior leaflet interscallop separation that is strongly associated with annular dilation. Clearly, IMR embodies a heterogeneous set of leaflet perturbations, and clinical studies corroborate the supposition that IMR and FMR may be associated with different leaflet deformations, although considerable overlap may occur on the clinical spectrum of disease. It is therefore not surprising that leaflet tenting, which represents the sum effect of annular and subvalvular geometric deformations on leaflet coaptation, is consistently identified in FMR and IMR as the main predictor of the severity of regurgitation.

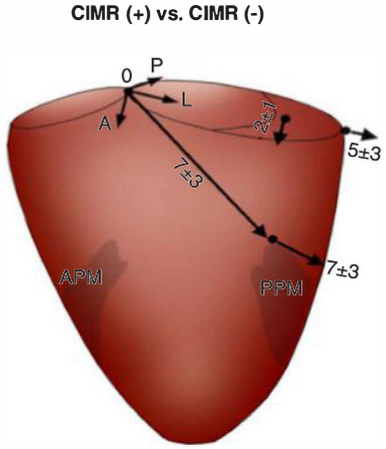



**FIGURE 34-8** Comparison of valvular geometric perturbations in the sheep that did [chronic ischemic mitral regurgitation—CIMR(+)] and did not [CIMR(−)] develop significant IMR 7 weeks after posterolateral myocardial infarction. Arrows indicate changes from baseline in the CIMR(+) group that were significantly different from changes in the CIMR(−) group. Annular enlargement and posterior papillary muscle displacement resulted in apical tethering of the posterior mitral leaflet associated with significant mitral regurgitation (P, posterior; L, lateral; A, apical; APM, anterior papillary muscle; PPM, posterior papillary muscle). (Reproduced from Tibayan FA, et al. *Circulation* 2003;108(Suppl 1):II116–II121.)

## SUMMARY

The mitral valve is a complex and dynamic structure that necessitates precise coordination of its constituents to achieve timely and efficient closure. Mitral pathophysiology may arise with dysfunction of the mitral annulus, mitral leaflets, the subvalvular apparatus, or a combination of these components resulting in mitral stenosis, regurgitation, or both. Although the pathophysiology of rheumatic mitral stenosis and degenerative mitral regurgitation has been well characterized, FMR and IMR continue to challenge scientists and surgeons alike. Further clinical and experimental studies are needed to better define the mechanisms of these vexing entities so that more effective reparative techniques can be developed and ultimately patient outcomes improved.

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## MITRAL VALVE PATHOPHYSIOLOGY BOARD REVIEW QUESTIONS (CHAPTER 34)

1. Which of the following is true regarding mitral valve anatomy?
   A. The right fibrous trigone is part of the central fibrous body of the heart.
   B. The highest point of the mitral annulus is at the commissures.
   C. The mitral annulus increases in size during early systole.
   D. The posteromedial papillary muscle is larger and typically has one major head.
   E. Second-order chordae prevent leaflet prolapse.

2. Which is accurate according to Carpentier classification of the mitral valve?
   A. Type IIIb = excessive motion during systole
   B. Type I = isolated leaflet prolapse
   C. Type II = annular dilation
   D. Type IIIa = excessive motion during diastole
   E. Type IIIb = ischemic mitral insufficiency
3. Which is correct concerning degenerative mitral insufficiency?
   A. There is excessive fibroelastic tissue in the elderly.
   B. The spongy connective tissue can affect the chordae tendineae.
   C. The annulus is not involved.
   D. Most patients with prolapse eventually develop symptoms.
   E. Chordal rupture in older patients is almost always associated with combined anterior and posterior leaflet pathology.
4. Which is true regarding IMR?
   A. Sphericity does not accompany recurrent MR after ventricular reduction surgery.
   B. IMR is solely dependent on global LV dilation.
   C. An anterior infarction produces substantially reduced ejection fraction compared with an inferior infarction.
   D. A small posterolateral infarction has little effect on the subvalvar apparatus.
   E. Reverse remodeling is more predictable if the LV exceeds 65 mm.
5. Which is correct in IMR?
   A. There is decreased motion of the lateral annulus.
   B. Isolated papillary muscle dysfunction typically causes substantial MR.
   C. Diastolic dysfunction of the inferior wall is the prerequisite lesion for clinical IMR.
   D. IMR results in decreased coaptation depth.
   E. Valvular tenting is not present in IMR.

## ANSWERS

1. **Answer: A.** The right fibrous trigone is part of the central fibrous body of the heart. The commissures are the lowest point of the annulus. The mitral annulus decreases rapidly in size during early systole. The anterolateral papillary muscle is larger and typically has one major head. First-order chordae prevent leaflet prolapse.
2. **Answer: E.** The classification system is as follows: type I = normal leaflet motion, type II = leaflet prolapse or excessive motion, type III = restricted leaflet motion. Type IIIa = restriction during diastole, type IIIb = restricted during systole.
3. **Answer: B.** The spongy connective tissue can affect the chordae tendineae in addition to the valve leaflets. There is fibroelastic deficiency in the elderly. The annulus is commonly involved, becoming thickened and dilated. Most patients with isolated prolapse will not develop symptoms. Chordal rupture in older patients is usually associated with P2 prolapse; combined leaflet pathology is least common.
4. **Answer: C.** An anterior infarction produces greater LV and mitral annular dilation and depresses LV function more than an inferior infarction. Sphericity does accompany recurrent MR after ventricular reduction surgery. IMR is not dependent on global LV dilation but rather on a localized LV insult. A small posterolateral infarction can have significant effect on the subvalvar apparatus. Reverse remodeling is more predictable if the LV is smaller than 65 mm.
5. **Answer: A.** The lateral annulus exhibits decreased motion in IMR. Isolated papillary muscle dysfunction does not result in significant MR. Systolic dysfunction of the interior wall is the prerequisite lesion for IMR. IMR results in increased depth of coaptation, and valvular tenting is an important clinical predictor of effective regurgitant orifice.

# 35 Mitral Valve Replacement

*Stephen J. Huddleston*
*David D. Yuh*

**KEY CONCEPTS**

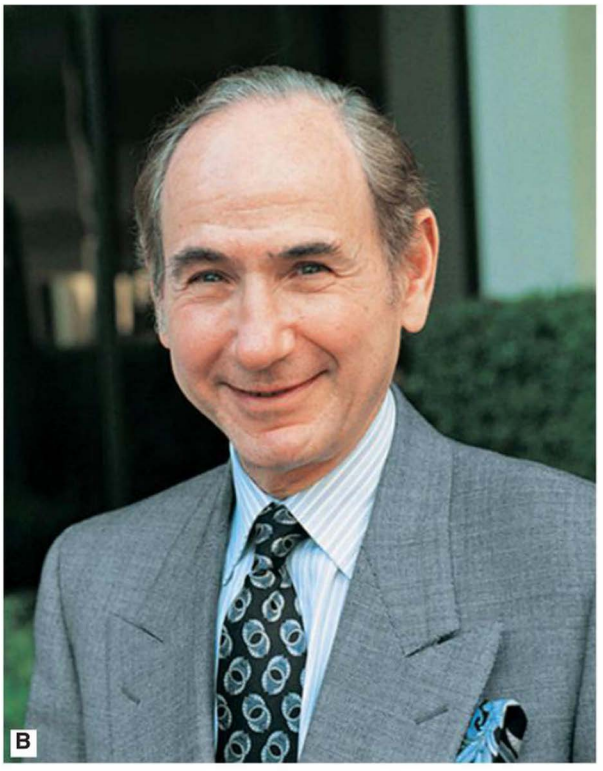
- Prosthetic valve design
  - Design of both mechanical and bioprosthetic valves has continued to evolve since the invention of the first valve to improve flow dynamics, reliability, and durability, while minimizing thrombogenicity and avoiding structural valve dysfunction (SVD).
- Indications
  - Mitral valve (MV) surgery is recommended for symptomatic acute severe mitral regurgitation (MR), chronic severe MR with New York Heart Association (NYHA) class II, III, or IV symptoms and no severe left ventricular (LV) dysfunction, and asymptomatic patients with mild-to-moderate LV dysfunction and severe MR. MV surgery is reasonable for asymptomatic severe MR in some cases. Mitral replacement in the setting of MR should be performed when repair is not possible or the functional result would be inadequate.
  - The indications for MV replacement in mitral stenosis are the following: (1) moderate (mean valve area ≤1.5 $cm^2$) or severe MS (mean valve area ≤1.0 $cm^2$) and NYHA functional class III or IV symptoms if they are not candidates for percutaneous balloon valvotomy or MV repair; and (2) severe MS with moderate-to-severe MR in symptomatic patients. MV replacement may be indicated for patients with severe MS with pulmonary hypertension and NYHA class I or II symptoms.
- Treatment (surgical)
  - The choice of prosthetic valve type is rooted in an understanding of valve features that determine thrombogenicity (the need for anticoagulation) and durability, as these factors relate to patient characteristics.
  - The most appropriate surgical approach to the MV is determined by patient characteristics and surgeon expertise. Typically, a median sternotomy, right thoracotomy, or mini right thoracotomy is employed. Aortic or femoral arterial cannulation and bicaval or femoral venous cannulation is performed depending on the incision. Venting may be performed through the aortic root and left atrium or left ventricle across the valve, and cardioplegia is given antegrade and retrograde. The valve may be exposed through a transverse incision in the left atrium or through a transseptal approach.
  - The chordal sparing technique of MV replacement improves LV function and survival. Valve stitches may be everting or noneverting.
  - Warfarin therapy with a goal INR of 2.5 to 3.5 is indicated after MV replacement with a mechanical prosthesis. Early anticoagulation for patients with bioprosthetic MVs is controversial.
- Outcomes/prognosis
  - MV replacement can be performed with outstanding efficacy, and risk is proportional to patient and surgical risk factors that can be assessed using well-established risk scoring systems. Acute surgical complications typically arise from problems with cardiopulmonary bypass or a combination of technical mistakes and patient factors. Late complications are rare and usually include prosthetic valvular endocarditis, thrombosis/anticoagulation, or SVD.

## INTRODUCTION

### History of Mitral Valve Replacement

The advent of cardiopulmonary bypass in 1953 opened the door for open cardiac surgery, but the first mitral valve (MV) replacement was not performed until 1959 at the National Heart Institute by Nina Starr Braunwald (Fig. 35-1A), the first woman to perform cardiac surgery.[1] Modeling anatomy, she designed the valve using flexible polyurethane with Teflon chordae. The patient was discharged from the hospital and did well clinically for several months. However, Albert Starr (Fig. 35-1B), a cardiac surgeon in Portland, OR, and Miles "Lowell" Edwards (Fig. 35-1C), an engineer in California,



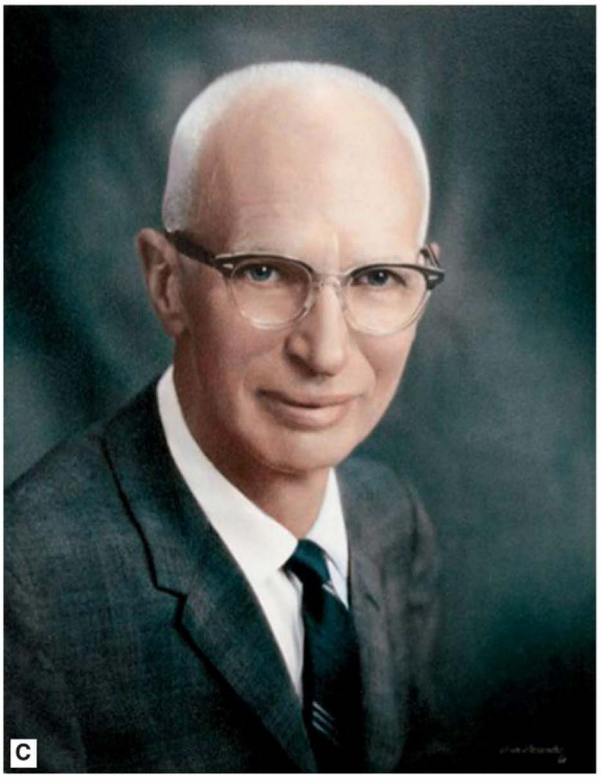




**FIGURE 35-1** Nina Starr Braunwald (**A**), the first surgeon to perform mitral valve replacement (**A**: Courtesy of the National Library of Medicine). Albert Starr (**B**) and Lowell Edwards (**C**) designed the caged-ball Starr–Edwards mechanical valve, which was the standard mechanical mitral valve for the first decade of mitral valve replacement (**B, C**: Reproduced with permission from Edwards Lifesciences, Irvine, California).

abandoned the approach of mimicking the native valve structure and instead focused on valve function to develop a more hemodynamically consistent and durable valve made from a silastic ball contained within a wire cage a rising from the valve housing.[2] This design debuted amidst a plethora of unique and distinct valve designs and revolutionized valve replacement, remaining the gold standard for MV replacement for much of that decade.

In pursuit of better hemodynamics and reduced thrombogenicity, the search for the perfect valve led to the development of other types of mechanical valves.[3] Tilting disk valves were introduced by Jura Wada in 1966 (Wada hingeless) and by C. Walt Lillehei and Robert Kaster in 1967 (Lillihei–Kaster). Viking Björk worked with the Shiley laboratories to develop the Björk–Shiley tilting disk valve that gained widespread application in the 1970s. Unfortunately, this valve had a propensity for thrombosis. After the disk design was changed to decrease thrombogenicity, the struts became susceptible to fracture. The valve was subsequently taken off of the market and many were removed from patients. The Medtronic-Hall tilting disk valve introduced in 1977 was the most commonly used tilting disk valve until it was recently taken off of the market in the United States. The most commonly used mechanical valve in the world today is the St. Jude mechanical bileaflet valve first introduced in 1977.

Driven by the problem of thrombogenicity of mechanical valves, work on bioprosthetic valves yielded the Carpentier and Hancock porcine xenografts in 1969,[4,5] and Marian Ionescu introduced a glutaraldehyde-fixed bovine pericardial valve in 1971.[6] These valves had promising early success, but structural valve dysfunction (SVD) was soon recognized to be a common complication, especially in younger patients. Further modification in the design and development of bioprosthetic valves has led to somewhat improved hemodynamics and durability, but SVD remains an obstacle to the use of these valves, especially in younger patients.

## INDICATIONS FOR REPLACEMENT VERSUS REPAIR

### Mitral Regurgitation

Because of improvements in MV repair techniques, repair of acquired mitral regurgitation (MR) is now usually feasible and durable, with improved left ventricular (LV) function, operative mortality, and long-term survival compared to MV replacement.[7] When repair is possible, survival is clearly better than with replacement if the MR is due to rheumatic, mixed, or degenerative disease, although the benefit of mitral surgery in ischemic MR is not as clear.[8] According to the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines, mitral surgery is recommended for symptomatic acute severe MR, chronic severe MR with New York Heart Association (NYHA) class II, III, or IV symptoms and no severe LV dysfunction, and asymptomatic patients with mild-to-moderate LV dysfunction and severe MR.[9] Level II evidence suggests that MV surgery is reasonable for asymptomatic severe MR in some instances. The primary indication for mitral replacement in the setting of MR is when repair is not possible or the functional result would be inadequate. This may be due to valve pathology that prohibits repair, a failed attempt at repair, or surgeon experience. Pathologic and anatomic factors that may make replacement preferable to repair include rheumatic MR, the presence of calcific deposits, and shortened chordae or papillary muscles. In patients with endocarditis, destruction of the valve annulus, leaflets, chordae, or papillary muscles may preclude repair. The management of mitral valvular endocarditis is discussed in detail in Chapter 38, but repair is generally preferable to replacement when possible, although destruction of the valve apparatus may make repair impossible.[10]

### Mitral Stenosis

As opposed to MR, acquired mitral stenosis (MS), usually due to rheumatic disease, more often requires replacement because the pathologic effects on the valve apparatus are not amenable to repair. According to the ACC/AHA Guidelines, the indications for MV replacement in MS are the following: (1) moderate (mean valve area $\leq$1.5 cm$^2$) or severe MS (mean valve area $\leq$1.0 cm$^2$) and NYHA functional class III or IV symptoms if they are not candidates for percutaneous balloon valvotomy or MV repair; and (2) severe MS with moderate–severe MR in symptomatic patients. Some evidence supports MV replacement in patients with severe MS with pulmonary hypertension and NYHA class I or II symptoms.[9] Retrospective data suggest that the outcome with replacement for MS is better than with MV commissurotomy and valvuloplasty.[11]

## CHOICE OF VALVE TYPE

### Hemodynamic Evaluation of Prosthetic Valves

The perfect valve remains elusive, but several characteristics define the ideal valve:

- Minimal pressure drop
- Trivial regurgitation
- Minimal turbulence and stasis
- Absence of shear stress
- Lifelong durability
- Biologically inert
- Negligible thrombogenicity

All of these characteristics are related to valve hemodynamics to varying degrees. For example, greater turbulence and stagnation can contribute to thrombogenicity and shear stress can lead to hemolysis. These forces can damage tissue

valves and contribute to calcification of all valve types and SVD of bioprosthetic valves. Therefore, a basic understanding of the hemodynamic assessment of prosthetic valves is fundamental to understanding the evolution and comparison of different types of prosthetic valves.[3,12,13] The normal valve area of the MV is 4 to 6 $cm^2$. The prosthetic valve housing, stent, and any other components that are within the housing decrease the true cross-sectional valve area through which blood must flow, defined as the effective orifice area (EOA). Therefore, the functional orifice of the valve, the EOA, is less than the geometric cross-sectional area of both the native annulus and the housing, and this will confer an inherent resistance and pressure gradient. The EOA may be determined by the Gorlin formula (derived from catheterization data and a hydraulic formula) or by the continuity equation, derived from acquired Doppler data.

These formulas are useful in comparing different valves in the laboratory. In the clinical setting, replacing a valve with an undersized prosthesis and a relatively small EOA relative to the patient size, also known as patient–prosthesis mismatch (PPM), is an area of controversy. One recent retrospective analysis from a single institution found that PPM was associated with recurrent congestive heart failure, postoperative pulmonary hypertension, and decreased survival after MV replacement.[14] Another large retrospective study found that PPM predicted higher mortality at 6 and 12 years after MV replacement.[15] However, no prospective data correlate EOA–patient size mismatch with long-term morbidity and mortality.

Another important parameter in evaluating hemodynamic function of prosthetic valves is the performance index, the ratio of the EOA to the sewing ring of the valve. The performance index is a surrogate measure for how efficiently the valve employs the total geometric area.

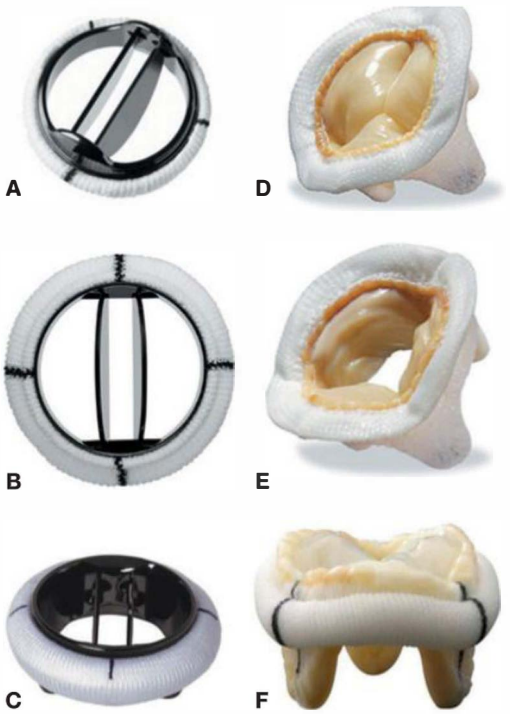



**FIGURE 35-2** Commonly used mechanical (**A–C**) and bioprosthetic (**D–F**) valves include the St. Jude mechanical (**A**: Permission to reproduce this image granted by St. Jude Medical, Inc.), Medtronic ATS Open Pivot Standard (**B**: Image reproduced with permission from Medtronic, Inc. Copyright Medtronic, Inc.), and On-X Mitral Standard (**C**: Image reproduced with permission from On-X Life Technologies, Inc.). Commonly used bioprosthetic valves include the Medtronic Hancock II (**D**: Image reproduced with permission from Medtronic, Inc. Copyright Medtronic, Inc.) and Mosaic (**E**: Image reproduced with permission from Medtronic, Inc. Copyright Medtronic, Inc.), as well as the St. Jude Biocor mitral valve (**F**: Permission to reproduce this image granted by St. Jude Medical, Inc.).

## Prosthetic Valve Types

Prosthetic valves are classified as either mechanical or bioprosthetic. Historically, the types of mechanical valves are caged ball, tilting disk, and bileaflet valves, although only bileaflet valves are currently available in the United States. These include the St. Jude mechanical (Fig. 35-2A), Sorin mechanical bileaflet, Medtronic ATS Open Pivot (Fig. 35-2B), and On-X Mitral Standard (Fig. 35-2C). Although both stented and stentless bioprosthetic valves have been used for MV replacement,[16] long-term follow-up is only available for stented bioprosthetic valves in the mitral position. Currently available bioprosthetic valves in the United States include the Carpentier–Edwards Perimount Magna pericardial bioprosthetic valve, Medtronic Hancock II (Fig. 35-2D) and Mosaic (Fig. 35-2E), as well as the St. Jude Epic mitral bioprosthetic valve (Fig. 35-2F). Homograft valves are not widely used for MV replacement. More than 50 different prosthetic valves have been introduced in the last 60 years. Unfortunately, insufficient data comparing different prosthetic valves in a prospective, randomized fashion exist to support the use of one type of valve over another. The individual characteristics of many of the different valves have been reviewed elsewhere.[3,17]

### MECHANICAL VERSUS BIOPROSTHETIC VALVES

Both patient and valve-related factors enter into the decision of whether to use a mechanical or a bioprosthetic valve.[17–19] Typically, mechanical valves have greater durability; however, they require lifelong anticoagulation. Bioprosthetic valves, on the other hand, are prone to SVD, but they are less thrombogenic and do not require anticoagulation. Hence, younger patients (<65–70 years old) are usually best served by a mechanical valve in order to avoid a reoperation for replacement of the bioprosthetic valve. However, patients who have contraindications to anticoagulation cannot have a mechanical valve. For example, women of child-bearing age who wish to conceive should

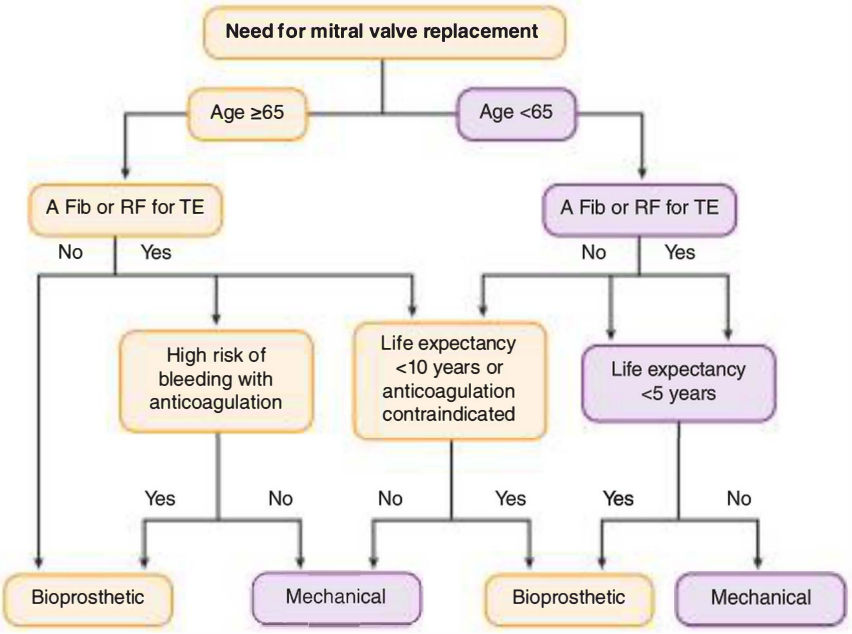



**FIGURE 35-3** An algorithm for the selection of mechanical versus bioprosthetic valves. A Fib, atrial fibrillation; RF, risk factor; TE, thromboembolism.

receive a bioprosthetic valve, and then after they are no longer planning on becoming pregnant, can undergo reoperation and replacement with a mechanical valve. Patients who are likely to be noncompliant with anticoagulation should also receive bioprosthetic valves. A patient at higher risk for bleeding complications with anticoagulation should receive a bioprosthetic valve. Alternatively, if a patient already has another indication for anticoagulation, such as atrial fibrillation, a mechanical valve does not present any additional risk. However, an older patient may be at increased risk of hemorrhagic complications, so a bioprosthetic valve may be indicated. Bioprosthetic valves may be sufficient for young patients with reduced longevity such as recalcitrant intravenous drug abusers and patients on permanent hemodialysis. Technical factors must also be considered, such as a small LV cavity that may not accommodate the stents of a bioprosthetic valve. An algorithm for selection of a prosthetic valve is presented in Figure 35-3. Clearly, the decision of whether a mechanical or bioprosthetic valve should be used is complex and should involve the patient, the cardiologist, and the cardiac surgeon.

# SURGICAL TECHNIQUE

## Surgical Approach

The MV may be approached through a median sternotomy, a right thoracotomy, an upper mini-sternotomy, a mini right thoracotomy, or robotically. The most appropriate incision or approach depends on patient factors such as previous operations, surgeon experience, and the need for combination with other procedures such as coronary artery bypass or aortic valve replacement. A median sternotomy is required when coronary artery bypass is performed in addition to MV replacement or in combined aortic valve and MV replacement. A right lateral, anterolateral, or posterolateral thoracotomy through the fourth intercostal space is particularly useful in a patient who has had a previous sternotomy and who does not require coronary artery bypass or aortic surgery. Minimally invasive MV surgery is gaining acceptance, and with appropriate surgeon experience, the MV may be exposed through a mini right thoracotomy with reduced blood loss and fewer transfusions.[20] The mini upper sternotomy has been described for mitral surgery but is much less commonly used.

## Combined Procedures

When MV replacement is combined with other procedures, the order of procedures is of critical importance so as to prevent the devastating complication of atrioventricular groove dissociation. If MV replacement is combined with coronary artery bypass, the distal anastomoses should be performed before valve replacement. Hemostasis of the distal anastomoses should be confirmed before MV replacement in order to avoid lifting the heart afterward, since this may cause an atrioventricular groove tear. If MV replacement is performed in combination with aortic valve replacement, the aortic valve should be excised first, followed by sequential replacement of the mitral and aortic valves.

## Cannulation and Cardiopulmonary Bypass Strategy

The strategy for arterial and venous cannulation depends on the surgical approach. If MV replacement is performed through a sternotomy, the aorta will be cannulated and bicaval venous cannulation is employed with a right angle metal tip cannula placed in the superior vena cava and a straight or right angle metal tip cannula in the inferior vena cava. If a standard right thoracotomy is used, the venous cannulation may be central or peripheral depending on the exposure, and femoral arterial cannulation is used. If the approach is through a mini right thoracotomy, cannulation of the right internal jugular and right femoral vein is performed. Caval snares should be placed for inflow occlusion, especially if the transseptal approach to the MV is anticipated. In a reoperation, femoral or axillary arterial cannulation, in addition to femoral venous cannulation, may be safer. If a right minithoracotomy or robotic approach is used, femoral arterial cannulation is required. MV replacement usually requires cardioplegic arrest, achieved through antegrade and/or retrograde infusion of cardioplegia. Moderate hypothermia and topical cold saline or ice provides additional myocardial protection. In certain situations such as reoperative mitral surgery after coronary bypass with an internal mammary graft, ventricular fibrillatory arrest may be employed. Venting may be performed through the aortic root or with a LV vent temporarily placed across the prosthetic valve after completion of the replacement; this vent is removed just prior to closure of the atriotomy.

## Exposure of the Mitral Valve

After developing Sondergaard's groove, a transverse left atriotomy is placed posterior to the interatrial sulcus close to the MV. When the sternum is deep or the left atrium is small, several techniques have been described to optimize exposure.[21] As described by Brawley,[22] the right atrium may be incised from the right atrial appendage toward the inferior vena cava and then the atrial septum can be incised at the inferior aspect of the fossa ovalis and the incision is extended superiorly to meet the right atriotomy. If necessary, the superior vena cava may be transected for additional exposure. The transseptal approach has also been described by Khonsari using a transverse incision through the atria extending from the right atrial appendage, across the atrial septum and over the roof of the left atrium toward the right superior pulmonary vein. The atrial septal incision is extended posteriorly and laterally into the fossa ovalis. Care must be taken when dividing the atrial septum to avoid injury to the bundle of His.

## Technique of Replacement

The chordal sparing technique for MV replacement is preferable when possible because of the preservation of annuloventricular continuity and LV function with improved survival.[23,24] The extent of preservation of the subvalvular apparatus depends on the severity and pattern of disease. If possible, both the anterior and posterior leaflets with associated first- and second-order chordae should be preserved. This may involve preservation of the entire leaflet with imbrication and plication of the leaflet tissue to the annulus using the valve sutures. Alternatively, a portion of each leaflet is excised and then the remaining leaflet with the attached chordae is fixed to the annulus.

Several chordal sparing techniques have been described. The posterior leaflet may be preserved by excising a crescent-shaped portion of the valve, leaving a rim of leaflet along the posterior annulus and a rim of leaflet with the attached chordae (Fig. 35-4A). The leaflet rim with the attached chordae is then attached to the posterior annulus with the valve sutures. If the anterior leaflet can be preserved, the central portion of the leaflet without chordae is resected and the anterolateral and posteromedial aspects of the leaflet with the underlying chordae are preserved (Fig. 35-4A). In the technique described by David,[25] the residual portions of the anterior leaflet are then reattached to the annulus with the valve sutures. In the technique described by Nara,[26] the A1 and A3 portions of the anterior leaflet with the associated anterolateral and posteromedial chordae are attached to the mitral commissures with pledgeted 2-0 braided sutures (Fig. 35-4B). The anterior leaflet halves may also be transposed onto the posterior annulus as described by Fiekes. The anterior leaflet may be divided into "buttons" with the attached chordae[27] and these may be reattached anatomically to the anterior annulus (Khonsari I, Fig. 35-4C) or a central scallop of the anterior leaflet may be excised and the contiguous strip of the anterior leaflet that has been detached may be plicated to the anterior annulus with the valve sutures (Khonsari II, Fig. 35-4D) or with a running polypropylene suture. If the chordae are too fibrotic and foreshortened, they may be excised and artificial chordae may be constructed using 4-0 PTFE sutures placed between the papillary muscle heads and the annulus. In addition to maintaining LV function, preservation of the posterior leaflet and the associated subvalvular apparatus protects against atrioventicular groove separation and LV perforation.

The valve annulus is sized appropriately and interrupted, horizontal, everting, pledgeted mattress braided sutures are placed in the annulus (Fig. 35-4A–D). If the annulus is calcified or when using a bioprosthetic valve, nonevverting pledgeted mattress sutures may be used (Fig. 35-5). If the annulus is severely calcified, extensive debridement and reconstruction with an autologous pericardial or bovine pericardial patch may be required. Care must be taken during placement of sutures in the valve annulus to avoid injury to surrounding structures including the left circumflex artery, the coronary sinus, the left atrial appendage, the aortic valve and LV outflow tract (LVOT), the anterior mitral curtain, and the atrioventricular node. Also, care must be taken to avoid capturing the valve stent in one of

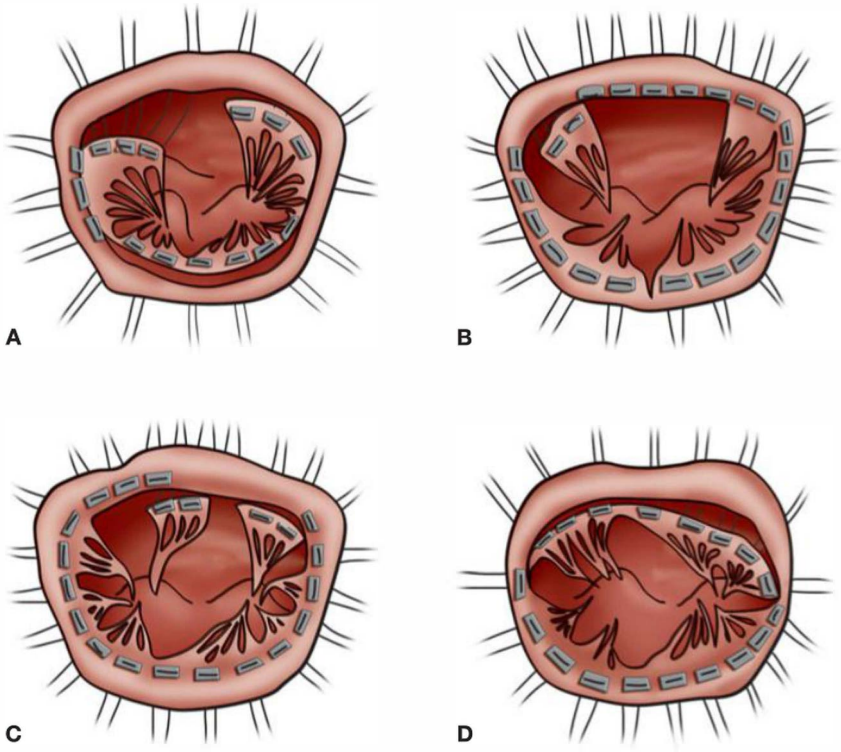



**FIGURE 35-4** Chordal sparing mitral valve replacement techniques as described by David (**A**), Nara (**B**), and Khonsari (I and II portrayed in **C** and **D**, respectively) using noneverting valve suture placement. (Illustration created by artist Shelley C. Griffin.)

the annular stitches. After the prosthetic valve is sutured in place, the leaflet motion should be evaluated to ensure that there is no interference with LV function and the LVOT is not compromised. An LV vent may be placed through the prosthetic valve before closing the atriotomy. Rewarming is completed and conventional de-airing maneuvers are performed. After leaving volume in the heart, the prosthetic valve function, LVOT, and completeness of de-airing are evaluated by transesophageal echocardiography (TEE). If there is no significant LVOT obstruction, mitral valvular regurgitation, or paravalvular leak, the patient is weaned from bypass.

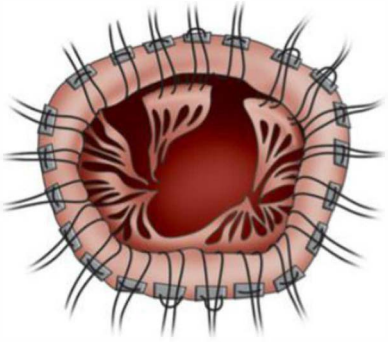


**FIGURE 35-5** Everting mattress sutures for valve fixation. (Illustration created by artist Shelley C. Griffin.)

## POSTOPERATIVE CARE AND OUTCOMES

### Anticoagulation

Warfarin therapy with a goal INR of 2.5 to 3.5 is indicated after MV replacement with a mechanical prosthesis.[9] Although the risk of thromboemboli remains 1 to 2 percent per year even with warfarin, it is much less than without. The risk of thromboembolism is higher with mechanical valves in the mitral position than in the aortic position, so the INR goal is higher for mechanical MVs than for aortic mechanical prosthetic valves.[9,28] The use of unfractionated heparin as a bridge to warfarin anticoagulation is controversial. If a patient with a mechanical valve has additional risk factors, aspirin 81 to 325 mg daily should be given in addition to warfarin. The On-X valve was found to have a low rate of thromboembolism even in the absence of or inadequate

anticoagulation,[29] and an ongoing trial is investigating outcomes with an INR of 2.0 to 2.5 plus aspirin 81 mg/day.

With a bioprosthetic valve in the mitral position, the risk of thromboemboli is only about 0.7 percent per year, although the risk has been reported to be higher during the first 3 months after replacement.[30] Anticoagulation is controversial for bioprosthetic MV replacements, and while some surgeons advocate warfarin anticoagulation for the first 3 months postoperatively, others do not anticoagulate unless there is another indication such as atrial fibrillation, previous thromboembolism, LV dysfunction (ejection fraction less than 30 percent), or a hypercoaguable condition.

Whenever a patient with a mechanical MV or a bioprosthetic valve with other risk factors for thromboemboli requires noncardiac surgery, an invasive procedure, or a dental procedure, the warfarin should be held and intravenous heparin should be started when the INR drops below 2.0.[9] The heparin is held for 4 to 6 h before the procedure and restarted after the procedure when the risk of bleeding is thought to be acceptably low. The warfarin is then restarted and the heparin is continued until the INR reaches 2.0. In an emergency, fresh frozen plasma may be given to correct the INR rapidly.

## OUTCOMES AND COMPLICATIONS

More than 90 percent of patients who undergo MV replacement should experience a functional improvement in outcome with significant resolution of heart failure symptoms. The morbidity and in-hospital mortality for MV replacement depends on patient demographics, risk factors, previous cardiovascular history, preoperative condition, and operative status (e.g., first time versus reoperation). This risk may be assessed using data from the Society for Thoracic Surgery Database or the European Risk System in Cardiac Operations.[31,32] Because these tools depend on frequent calibration, dependent on multiple dynamic factors, they must continuously be updated to maintain accuracy. Predictors of a poor outcome include advanced patient age, poor functional class, coronary artery disease, reoperative status, and emergency operations. Common causes of early operative mortality include stroke, myocardial infarction, respiratory failure, multisystem organ failure, and infection. Stroke may still occur later, and other late causes of postoperative mortality include persistent heart failure and complications related to thromboemboli. The risk of hemorrhage due to anticoagulation is proportional to the degree of anticoagulation.

The outcome of mechanical valve replacement has improved dramatically with adoption of chordal sparing techniques and preservation of ventriculoannular continuity. Conversely, technical misadventures can lead to devastating complications. Paravalvular leak will lead to persistent MR with heart failure and possibly hemolysis. If a paravalvular leak is detected on intraoperative TEE, cardiopulmonary bypass should be reinstituted and the cause corrected.

LV rupture is an uncommon but often fatal complication. In a retrospective analysis by Deniz and colleagues, the incidence of posterior ventricular rupture after MV replacement was 0.8 percent, and risk factors included age greater than 60, female gender, reoperation, and resection of the posterior leaflet.[33] None of the patients in that series who had preservation of the posterior leaflet had LV rupture. LV rupture may occur at the level of the annulus, at the base of an excised papillary muscle, or between the papillary muscle and the annulus. Excessive traction on the annulus and overzealous debridement of annular calcifications should be avoided in order to minimize the risk of LV rupture. After valve replacement, lifting of the heart should be avoided to prevent LV rupture. If LV rupture occurs, the patient should be placed back on cardiopulmonary bypass immediately and the prosthetic valve should be removed in order to gain access to the LV rupture. A bovine pericardial patch is sutured to the ventricular endocardium and used to reconstruct the annulus. After the prosthetic valve is resutured in place using pledgeted sutures, the atrial edge of the bovine pericardial patch is sutured to the atrial endocardium. Atrioventricular groove hematoma or disruption is another rare complication similar to LV rupture often related to extensive debridement and decalcification of the annulus and posterior leaflet.

In addition to thromboembolic and bleeding complications due to anticoagulation, several other valve-related complications may occur after MV replacement. The risk of SVD is inversely proportional to the age of the patient (especially <65 years of age) and is more common in the mitral than in the aortic position.[34,35] SVD begins at about 5 years after MV replacement, and the incidence increases significantly after 10 years. The only treatment for SVD is reoperation with re-replacement of the valve prosthesis. Transcatheter valve-in-valve implantation has been reported for the treatment of SVD of bioprosthetic valves in the mitral position.[36]

Valve thrombosis in the absence of infection with obstruction of flow through the valve or interference with valve function has an incidence of 0.5 percent after MV replacement.[37] The presentation of valve thrombosis ranges from subtle findings to cardiogenic shock. Traditionally, valve thrombosis was an indication for emergent surgical thrombectomy with possible replacement of the prosthetic valve, but thrombolysis is increasingly considered the first-line treatment, although embolic complications are a concern.

The risk of prosthetic valvular endocarditis (PVE) is highest in the first 3 months after replacement and is slightly greater for mechanical than for bioprosthetic valves. The risk of early PVE is about 1 percent in the first 12 months, and the risk of late PVE is 0.2 to 0.35 percent per patient-year. Bacteremia or contamination leading to PVE may occur intraoperatively or from placement of intravenous catheters, indwelling urinary catheters, invasive procedures, and wound infections.

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## MITRAL VALVE REPLACEMENT BOARD REVIEW QUESTIONS (CHAPTER 35)

1. MV replacement is indicated for:
   A. A 65-year-old man with dyspnea, severe MR, and posterior on echocardiography
   B. A 25-year-old man with recent intravenous drug abuse and mitral valvular endocarditis with an anterior leaflet vegetation greater than 1.5 cm in greatest dimension
   C. A 55-year-old woman with dyspnea with minimal activity and moderate MS with thickening of the leaflets and severe fibrosis and shortening of the chordae that is not amenable to percutaneous mitral balloon valvuloplasty
   D. A 70-year-old man with 3-vessel coronary artery disease, a non-ST-segment elevation myocardial infarction and ischemic mitral regurgitation

2. A bioprosthetic valve is preferable to a mechanical valve for MV replacement for:
   A. A 45-year-old man with severe MR and mitral valvular endocarditis with a 9-mm vegetation on the anterior leaflet and peripheral emboli despite treatment with antibiotics
   B. A 35-year-old woman with rheumatic heart disease and severe MS who wishes to conceive
   C. A 60-year-old man with atrial fibrillation on warfarin anticoagulation and severe MS
   D. A 55-year-old woman with severe MS

3. When performing combined aortic valve replacement (AVR), MV replacement and 2-vessel coronary artery bypass with the left internal mammary artery to the left anterior descending artery and a saphenous vein graft to the obtuse marginal branch of the left circumflex artery, the correct order of procedures is:
   A. Excise aortic valve, MV replacement, aortic valve replacement, distal anastomoses, proximal anastomosis.
   B. Distal anastomoses, excise aortic valve, aortic valve replacement, MV replacement, proximal anastomosis.
   C. Distal anastomoses, MV replacement, excise aortic valve, aortic valve replacement, proximal anastomosis.
   D. Distal anastomoses, excise aortic valve, MV replacement, aortic valve replacement, proximal anastomosis.

4. The chordal sparing technique of MV replacement has:
   A. Reduced the incidence of postoperative thromboembolic complications
   B. Not improved survival after MV replacement
   C. Been associated with increased risk of left ventricular rupture when the posterior leaflet is preserved
   D. Been associated with improved left ventricular function compared to the nonchordal sparing technique.

5. The risk of thromboembolic complications after MV replacement is:
   A. Higher in mechanical prosthesis with anticoagulation than with mechanical AVR with anticoagulation
   B. Less with a mechanical valve with anticoagulation than with a bioprosthetic valve without anticoagulation
   C. Not affected by poor ventricular function with a left ventricular ejection fraction less than 30 percent
   D. Is negligible in a patient with a mechanical valve and warfarin anticoagulation

## ANSWERS

1. **Answer: C.** MV replacement is indicated for moderate MS with NYHA class III symptoms when percutaneous mitral balloon valvuloplasty is not an option. MR with posterior leaflet prolapse is often amenable to repair, as is mitral valvular endocarditis not responding to medical therapy. Ischemic mitral regurgitation often responds to MR and usually does not require MV replacement.
2. **Answer: B.** A bioprosthetic valve is appropriate in a woman of child-bearing age who wishes to conceive. After the woman is has completed child bearing, she can undergo reoperation for replacement with a mechanical valve with postoperative warfarin anticoagulation.
3. **Answer: D.** When performing combined AVR and MV replacement with coronary artery bypass, distal anastomoses should be performed first. Next the aortic valve should be excised, since this can disrupt the MV replacement if it was done before excision of the aortic valve. After replacing the MV, the heart should no longer be lifted to minimize the risk of posterior LV rupture. The aortic valve replacement is then performed and the proximal anastomosis is performed last after closure of the aortotomy.
4. **Answer: D.** The chordal sparing technique of MV replacement has no impact on the incidence of postoperative thromboembolic complications, but LV function and postoperative survival are both improved. The risk of LV rupture is less with preservation of the posterior leaflet and the chordal sparing technique.
5. **Answer: A.** The risk of thromboembolic complications after mechanical MV replacement with anticoagulation is higher than with mechanical AVR with anticoagulation. Thromboembolic complications occur in 1 to 2 percent of patients after mechanical MV replacement despite anticoagulation with a goal INR of 2.5 to 3.5, compared to 0.7 percent of patients with a bioprosthetic MV replacement. Low LV ejection fraction (<30 percent), atrial fibrillation, previous thromboembolism, and a hypercoagulable state increase the risk of thromboembolic complications and are indications for the addition of aspirin to warfarin anticoagulation.

36

# Mitral Valve Repair for Degenerative Disease

*Gurjyot Bajwa*
*Tomislav Mihaljevic*
*A. Marc Gillinov*

**KEY CONCEPTS**

- Advantages of repair vs replacement
  - Degenerative disease of the mitral valve is a surgically treatable entity, when repaired leading to improved quality of life and better long-term survival as opposed to replacement.
- Keys to repair
  - Condition of the mitral valve
  - Experience of the surgeon
- Repair techniques
  - Choice of repair depends on the site of prolapse.
  - Tailor repair to site and mechanism determined by perioperative echocardiogram
- Surgical approaches
  - Range from complete sternotomy to robotically assisted
  - Choice of approach should be tailored to valve pathology determined preoperatively.
  - Standard, reproducible repair techniques should be employed.
- Outcomes
  - Durability of repair is measured by freedom from reoperation and recurrence of MR.
  - Operative risk is less than 1 percent.
  - Long-term survival rates at 10, 15, and 20 years are 92, 76, and 48 percent, respectively

## ADVANTAGES OF MITRAL VALVE REPAIR OVER REPLACEMENT

It is well accepted that the majority of patients with degenerative mitral valve disease who require surgery will have an improved quality of life with less morbidity and better long-term survival with valve repair as opposed to replacement.[1] This is attributable primarily to prosthesis-related morbidity, including higher reoperation rates, greater risk of endocarditis, and the need for anticoagulation with mechanical valves. Anticoagulation is particularly problematic for young, active patients and women in the child-bearing age group.

Therefore, when feasible, repair is preferred to replacement. The two keys to repair feasibility are the condition of the mitral valve and the experience of the surgeon. In most cases, mitral valve repair is technically no more complex than valve replacement. Mastery of only a handful of repair techniques enables repair of more than 90 percent of degenerative valves. A successful mitral valvuloplasty for degenerative disease provides most patients with an extremely durable valve, with many patients remaining free of reoperation 30 years after valve repair.[2]

## REPAIR TECHNIQUES

The choice of repair technique for a given mitral valve depends upon the site of prolapse. We will present, in sequence, repair options for posterior, anterior, commissural, and bileaflet prolapse.

### Posterior Leaflet Prolapse

Approximately 75 percent of patients with mitral regurgitation (MR) caused by degenerative disease have isolated prolapse of the posterior leaflet, most commonly the P2 segment (middle scallop).[3] Several techniques have been developed to deal with this anatomical site of prolapse.

## QUADRANGULAR RESECTION

This is the classic technique for managing P2 prolapse, with or without a sliding repair.[4] The sliding repair was developed to reduce the risk of postrepair systolic anterior motion (SAM) in the setting of excessive leaflet tissue and/or a small, hyperdynamic left ventricle.[5] The classic quadrangular resection, which includes annular plication, is rarely employed today and has been largely replaced by a triangular resection technique. Similarly, a folding repair technique has replaced the sliding repair.

## TRIANGULAR RESECTION

In the patient with segmental posterior leaflet prolapse, MR is caused by lack of leaflet coaptation at the site of posterior chordal rupture or elongation. Hence, it is logical to target the free edge of the prolapsing or flail leaflet.[6,7] A triangular resection comprises resection of the localized prolapsed or flail segment, with incisions in the leaflet angled toward one another as the incisions approach the annular level. No annular plication sutures are necessary. This simplified resection technique is particularly useful in minimally invasive right thoracotomy or robotic approaches as it saves operative time. As with most mitral repairs, this repair is completed with placement of a posterior flexible annuloplasty band (Fig. 36-1).

## FOLDING PLASTY

The folding plasty technique is used to treat posterior leaflet prolapse when there is a high risk of SAM, replacing the sliding repair for this indication.[8] The prolapsing portion of the posterior leaflet is resected as for a quadrangular resection, leaving tall posterior leaflet remnants on either side (Fig. 36-2). A suture is passed through the midportion of the cut leaflet edge on each side, and this suture is then passed through the annulus at the midportion of the area of resection; this maneuver reduces the posterior leaflet height. If necessary, suture placement is modified to ensure that the leaflet remnants are of similar height. Leaflet tissue is then approximated to the annulus, closing the gap at the annular level and uniformly reducing the height of the posterior leaflet in this region. The leaflet edges are reapproximated centrally and an annuloplasty band completes the repair.

## ARTIFICIAL CHORDAE

There is growing enthusiasm for the use of artificial chordae to correct posterior leaflet prolapse. The chordae are constructed from ePTFE (Gore-Tex, W.L. Gore and Assoc, Flagstaff, AZ).

Two general chordal replacement techniques may be used. Chordal loops can be fashioned and affixed to a papillary muscle, creating multiple new chordae (loops) of the same length; usually this length is approximately 10 mm when treating posterior prolapse. Each of the chordal loops is attached to the free edge of the prolapsing leaflet with a figure-of-eight suture. The chordae are spaced on the leaflet edge at distances of 7 to 10 mm.[9,10] (Fig. 36-3)

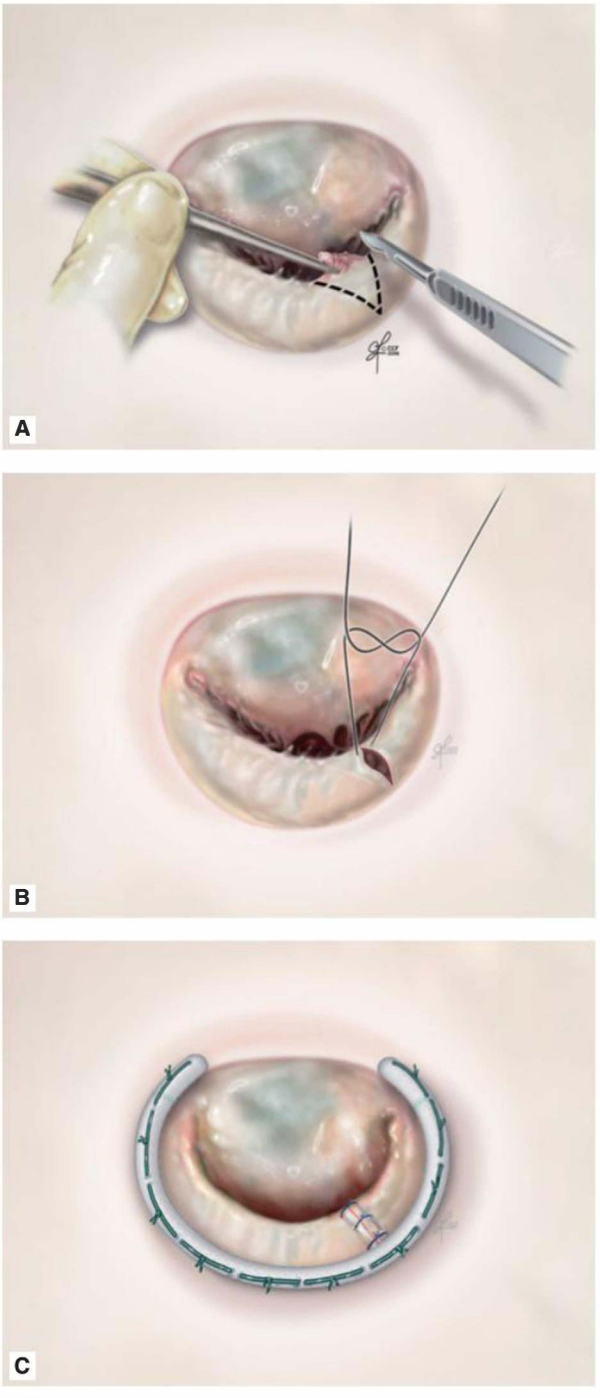



**FIGURE 36-1** Triangular resection. **A.** The prolapsing/flail segment of the posterior leaflet is identified and excised as a triangle. **B.** The leaflet edges are reapproximated. **C.** Annuloplasty completes the repair. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.)

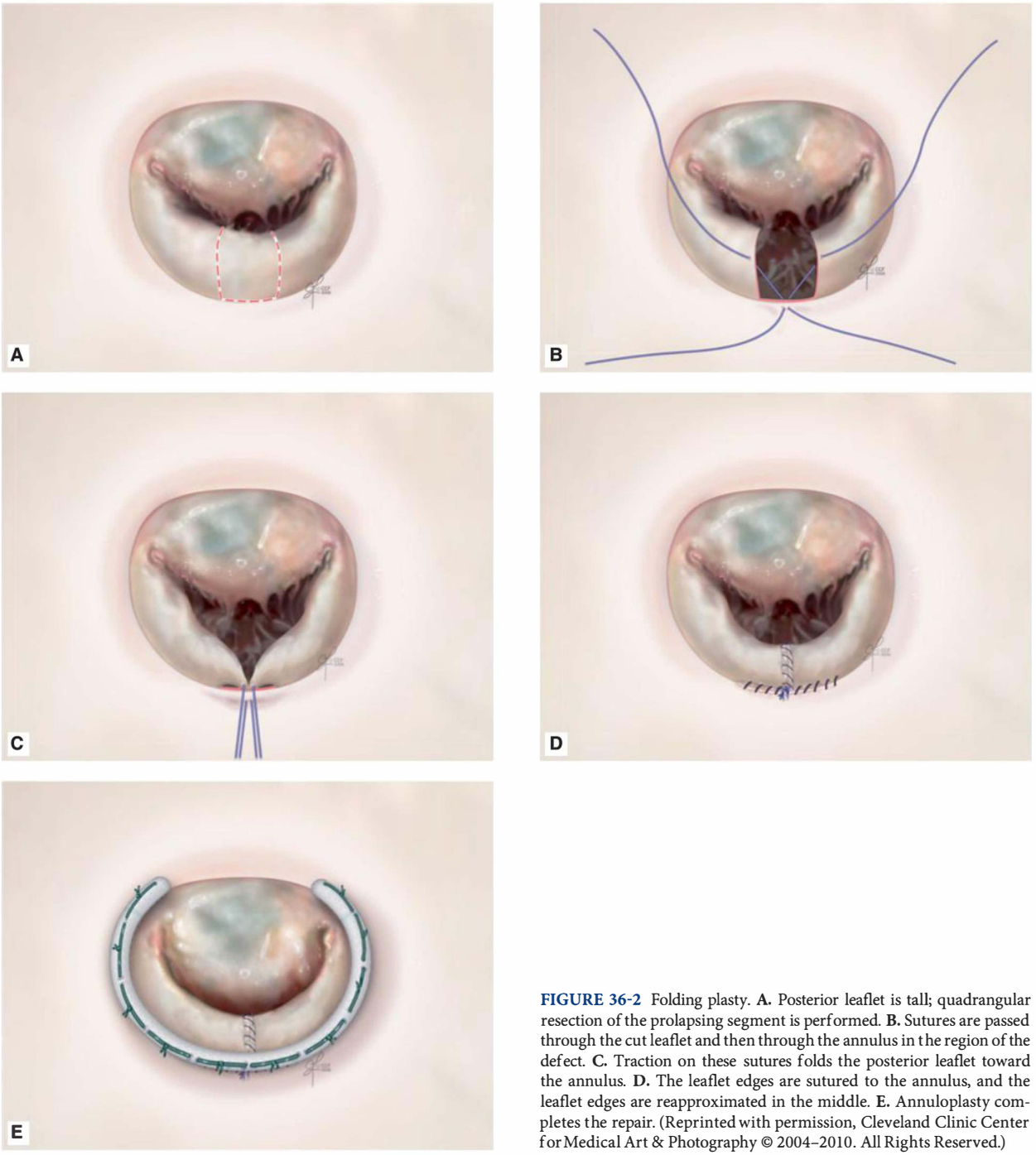



**FIGURE 36-2** Folding plasty. **A.** Posterior leaflet is tall; quadrangular resection of the prolapsing segment is performed. **B.** Sutures are passed through the cut leaflet and then through the annulus in the region of the defect. **C.** Traction on these sutures folds the posterior leaflet toward the annulus. **D.** The leaflet edges are sutured to the annulus, and the leaflet edges are reapproximated in the middle. **E.** Annuloplasty completes the repair. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.)

Alternatively, a figure-of-eight ePTFE suture is taken through the tip of a papillary muscle, and then each needle is brought up through the free edge of the leaflet twice, each time from the ventricular to the atrial side. The annuloplasty band is placed next. Then the ventricle is insufflated with saline and the chordae are adjusted to a length such that there is no leakage. Care is taken when tying the chordae at the leaflet edge, as excessive tension at tying will cause the chordae to be too short, resulting in leaflet restriction (Fig. 36-4).

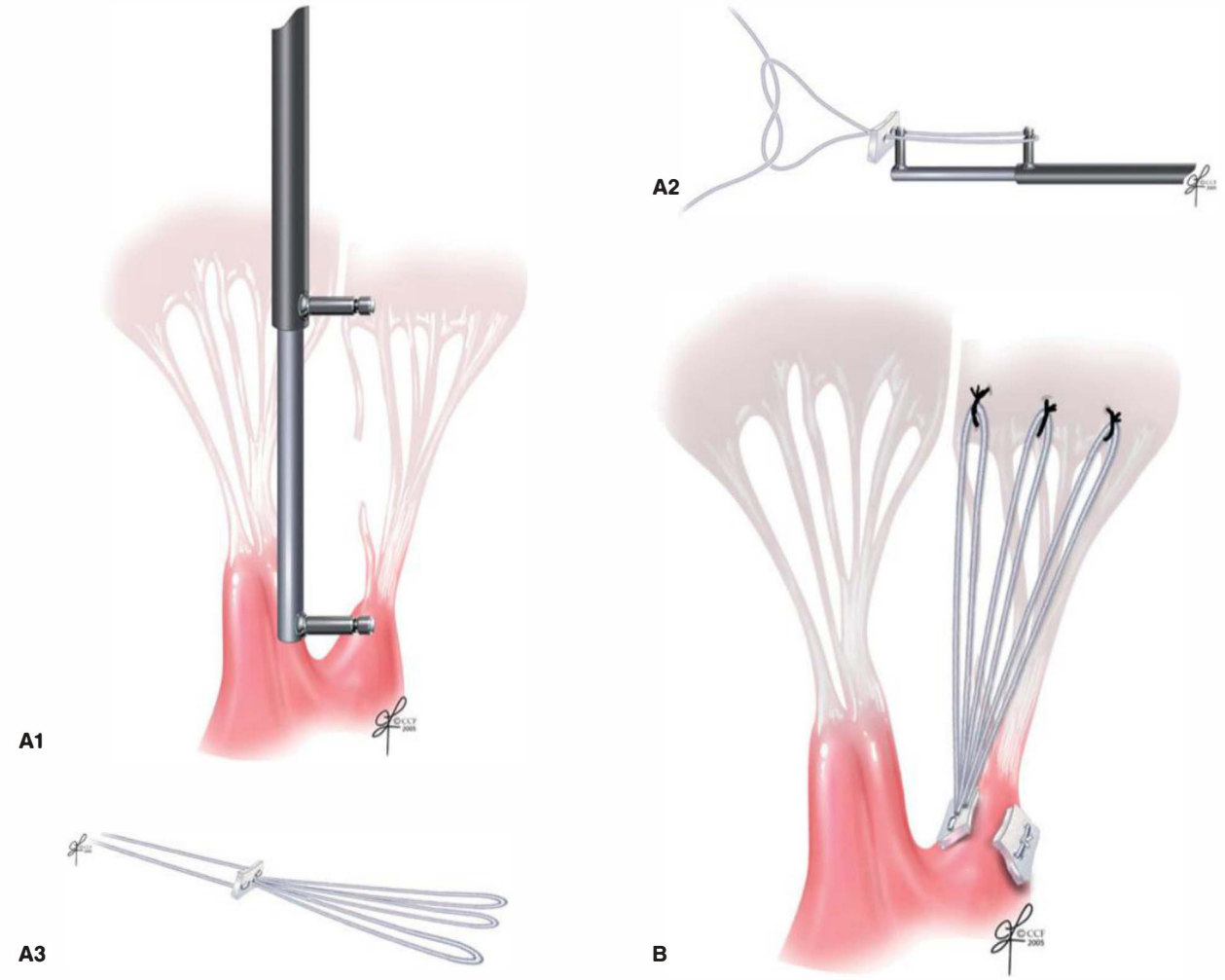



FIGURE 36-3 Creation of premeasured artificial chordae. **A.** Chordal loops are made after caliper measurement is taken. **B.** The loops are affixed to a papillary muscle and then individually to the free edge of the prolapsing segment of the leaflet. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.)

## Anterior Leaflet Prolapse

Anterior leaflet prolapse has traditionally posed a challenge for surgeons performing mitral valve repair. Repair techniques include artificial chordae, chordal transfer, commissuroplasty, and the Alfieri edge-to-edge repair. Freedom from reoperation after anterior leaflet repair has been inferior to that after posterior repair. There is no question that repair of P2 leaflet prolapse by posterior resection and annuloplasty is technically simpler than anterior leaflet repair. However, standardization of anterior repair through the use of artificial chordae provides a relatively simple and durable repair.

### ARTIFICIAL CHORDAE

The key challenge in using artificial chordae is the proper determination of chordal length; there are many techniques for estimating chordal length.[9,10] If chordal loops are used, the surgeon uses a caliper to measure the length of a normal chord from the head of the papillary muscle to the level of the annulus. Chordal loops of this length—usually 21 to 23 mm—are constructed, affixed to a papillary muscle and then to the free edge of the leaflet. Alternatively, the free-hand technique for chordal construction can be used. As with posterior leaflet prolapse, this involves a figure-of-eight ePTFE suture passed through the papillary muscle, followed by two passes through the free edge of the prolapsing leaflet, and tying the suture with the annuloplasty band in place and the ventricle filled with saline to assure valve competence.

### CHORDAL TRANSFER

This technique consists of excising a portion of the posterior leaflet with normal chordae and transferring it to

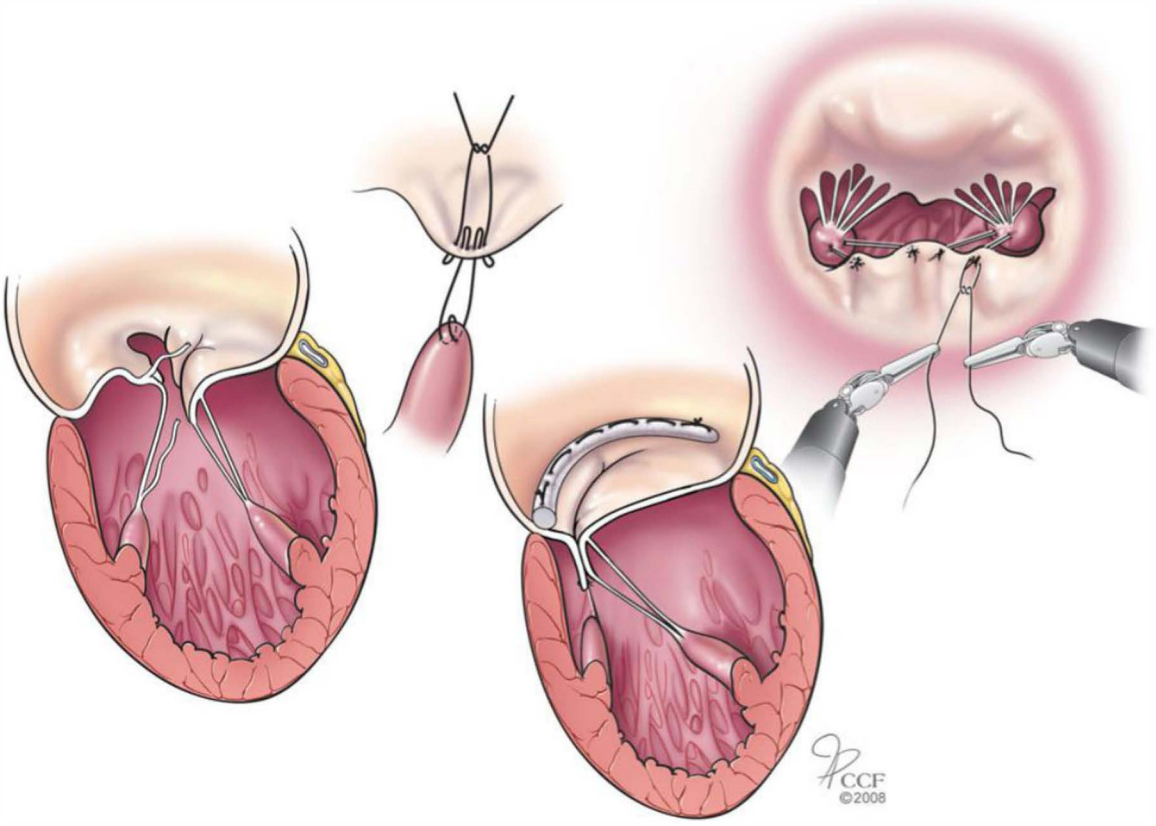



**FIGURE 36-4** Artificial chordae. Figure-of-eight-stitch through the papillary muscle, then through the free edge of the leaflet, with knots tied on the atrial aspect. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.)

support a portion of the anterior leaflet to which chordae have ruptured or elongated. Essentially, the posterior leaflet and its chords are "flipped over" to the anterior leaflet. The posterior leaflet is reconstructed in standard fashion and an annuloplasty band completes the repair (Fig. 36-5). The limitation of this technique is that it requires manipulation of a previously normal posterior leaflet in order to address anterior leaflet pathology. For this reason, we currently favor creation of artificial chordae to correct anterior leaflet prolapse.

### EDGE-TO-EDGE REPAIR

Described by Alfieri and coworkers, the edge-to-edge repair is the simplest maneuver for correction of prolapse.[11] With this technique, the prolapsing segment of the anterior leaflet is sutured to normal posterior leaflet directly opposite, ensuring coaptation and preventing prolapse. Sutures are taken several millimeters deep into the leaflet and span the entire region of prolapse. The suture line should not exceed 1 cm in length. Of note, the edge-to-edge technique can also be employed to manage posterior prolapse and bileaflet prolapse; however, it is rarely our primary repair technique for these pathologies.

## Commissural Prolapse

Commissuroplasty is a simple and reproducible technique for management of commissural prolapse involving the anterior, posterior, or both leaflets.[12] The edge of the prolapsing segment is sutured to the free edge of the opposite leaflet (Fig. 36-6). Care must be taken to avoid closing too much of the valve orifice. In addition, a relatively large annuloplasty band is employed to avoid mitral stenosis.

## Bileaflet Prolapse

Bileaflet prolapse is often a consequence of Barlow's disease. Management of this entity depends on valve pathology. Nearly all of these patients have excess leaflet tissue and annular dilatation. In many patients with bileaflet prolapse, the prolapse is asymmetrically distributed, with the predominant lesion being prolapse of the middle scallop of the posterior leaflet. This produces an anteriorly directed jet of MR. In such cases, mitral repair is most often achieved by a triangular resection of the P2 scallop. If the reconstituted leaflet height is extensive, a sliding repair or folding plasty is performed. A large annuloplasty ring completes the repair.

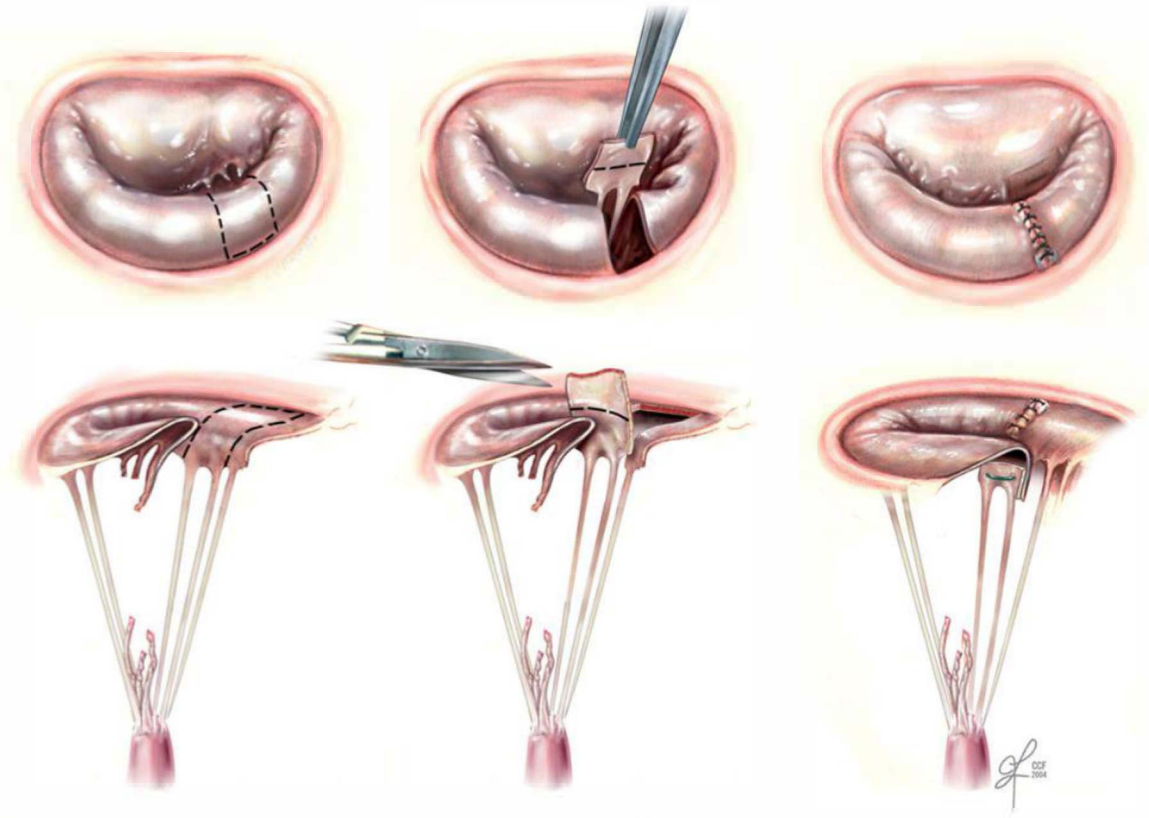


**FIGURE 36-5** Chordal transfer. A strip of posterior leaflet tissue with the attached normal chordae is transferred to the prolapsing free edge of the anterior leaflet. The posterior leaflet edges are reapproximated. Annuloplasty completes the repair. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.)

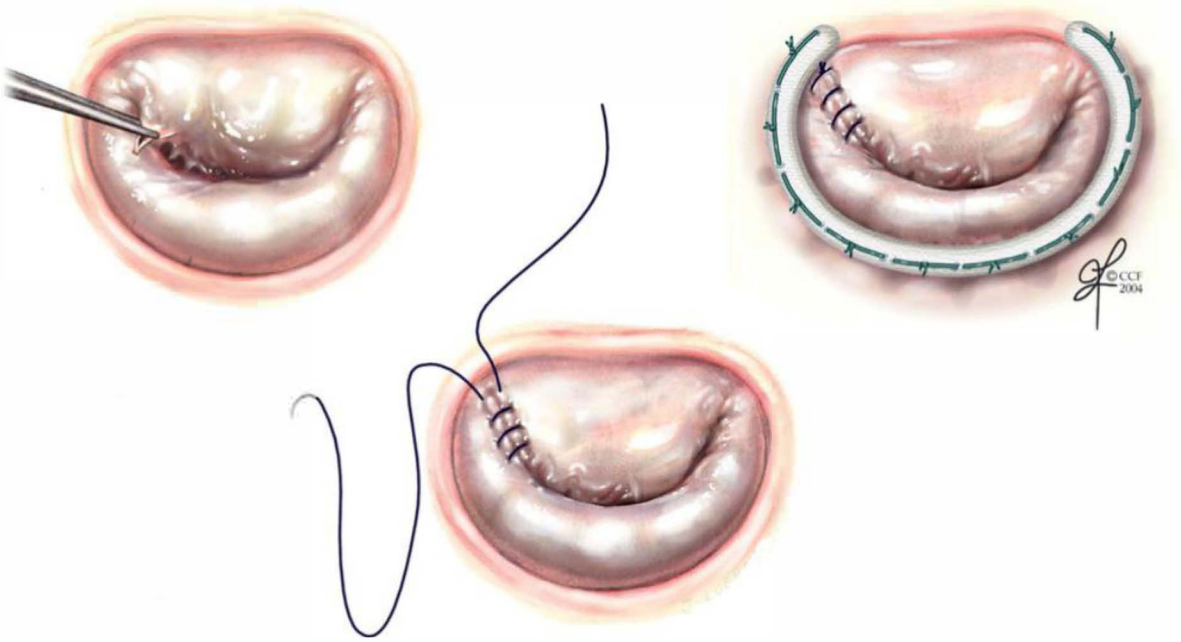


**FIGURE 36-6** Commissuroplasty. Commissure is closed with running suture. Annuloplasty completes the repair. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.)

In patients with symmetric bileaflet prolapse, a central jet of regurgitation, and no flail, repair can be achieved with a large annuloplasty device (36 mm or greater). This reduces annular diameter and increases leaflet coaptation. Although this is a simple technique, close attention must be paid to the height of the posterior leaflet to avoid postrepair SAM.

In patients with severe bileaflet prolapse, it is often necessary to address both leaflets, necessitating a combination of repair techniques (i.e., resection and sliding repair of the posterior leaflet, artificial chordae for the anterior leaflet, or chordae for both the anterior and posterior leaflet to suspend all valve segments, and annuloplasty to increase leaflet coaptation).

### Annuloplasty Devices

Annuloplasty is a component of all repairs for degenerative mitral valve disease. Use of a prosthetic annuloplasty improves repair durability.[13] Although there are many annuloplasty devices available—rigid vs flexible, complete vs partial—the truth is that all work well in patients with degenerative mitral valve disease. The surgeon should choose the annuloplasty device with which he or she is most comfortable.

## MITRAL VALVE REPAIR—SURGICAL APPROACHES

There are a variety of surgical approaches to repairing the mitral valve. The key decisions regarding choice of approach include safety and efficacy. Although a minimally invasive approach is desirable, it is only advisable if safety and effectiveness can be maintained.

### Complete Sternotomy

This is the standard approach for most cardiac operations. Central cannulation is achieved via the ascending aorta and the superior and inferior vena cavae. The heart is protected with both antegrade and retrograde cardioplegia. The mitral valve is exposed via a transverse left atriotomy anterior to the insertion of the right superior and inferior pulmonary veins.

### Right Mini-Thoracotomy

The right mini-thoracotomy approach is increasingly popular for treatment of patients with mitral valve dysfunction and can be employed in patients requiring concomitant management of atrial fibrillation or tricuspid regurgitation as well. Although minor variations abound, the most common approach includes a 4- to 8-cm skin incision in the inframammary crease lateral to the nipple and entry into the chest via the fourth intercostal space (Fig. 36-7). Patient preparation includes a double-lumen endotracheal tube and positioning with a roll placed under the right scapula; the right arm is distracted 5 to 10 cm to provide working room for the surgeon and to enable placement of a transthoracic aortic cross-clamp. After entry into the fourth intercostal space under single-lung isolation, a soft tissue retractor is placed to improve exposure and to protect the intercostal neurovascular bundle. A stainless steel rib retractor is positioned next. Occasionally the diaphragm obscures exposure of the pericardium near the inferior vena cava; a stay suture in the central tendon of the right hemidiaphragm, brought out through the fifth or sixth intercostal space, improves exposure. The pericardium is opened 3 cm or more anterior to the phrenic nerve, and stay sutures brought through the chest wall in the midaxillary line to retract the pericardial edge.

Cardiopulmonary bypass is established via peripheral cannulation. The anterior surfaces of the femoral artery and vein are exposed and cannulated with a modified Seldinger technique. Under transesophageal echocardiographic guidance, the tip of a long dual-stage venous cannula is advanced into the superior vena cava. The leading edge of the cannula should be advanced at least 4 cm into the superior vena cava to prevent migration back into the right atrium, which can lead to inadequate venous drainage and obscure exposure of the mitral valve. A femoral arterial cannula is also placed. Aortic occlusion is accomplished with a transthoracic cross-clamp inserted through the third intercostal space in the midaxillary line; alternative methods of aortic occlusion include a flexible clamp introduced into the field, or an endoaortic balloon introduced via the femoral arterial cannula and positioned with echocardiographic guidance.

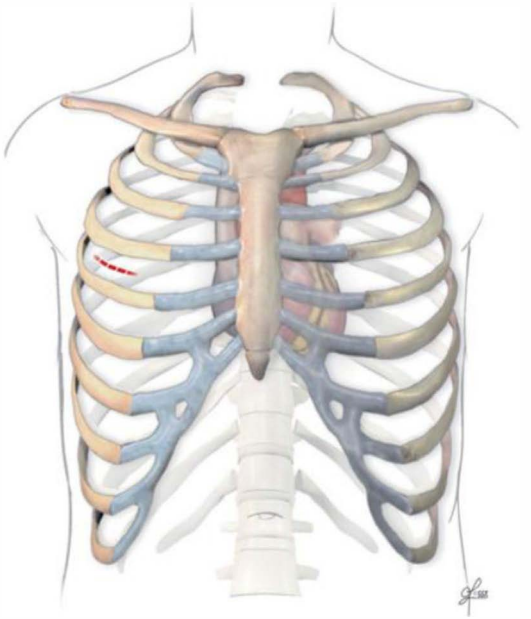


**FIGURE 36-7** Right mini-thoracotomy. A 6-to-8-cm incision in the fourth intercostal space, peripheral cannulation, antegrade and retrograde cardioplegia. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.)

We favor the transthoracic clamp when using the nonrobotic right mini-thoracotomy approach. Myocardial protection is achieved with antegrade cardioplegia (catheter placed directly in ascending aorta or endoaortic balloon) and is frequently supplemented by retrograde cardioplegia and systemic hypothermia. Some surgeons prefer to perform the operation under fibrillatory arreset and do not occlude the aorta or employ cardioplegia.

The mitral valve is approached via a standard transverse left atriotomy. A static retractor is placed through the third intercostal space lateral to the internal thoracic artery which lifts the interatrial septum and exposes the mitral valve. Long-shafted instruments are used to perform the repair. Placement of annuloplasty sutures before leaflet repair improves exposure, particularly in the region of P3. A knot-pusher is used to tie sutures as tying by hand is not possible with this approach.

Right thoracic approaches are contraindicated in patients with small femoral vessels (less than 7 mm), peripheral arterial disease, aortic regurgitation that is moderate or greater, and pectus excavatum. Preoperative testing should include a computed tomography (CT) scan to determine femoral vessel size and to rule out peripheral arterial disease.

## Robotically Assisted Right Thoracic Approach

Robotically assisted mitral valve repair entails a right thoracic approach. Mastery of standard, minimally invasive, nonrobotic right thoracotomy technique is mandatory before progressing to robotically assisted surgery. The robotic, port-based approach includes placing a working port in the fourth intercostal space anterior to the anterior axillary line and a camera port in the fourth intercostal space 2 to 3 fingerbreadths anterior to the working port. The left robotic arm is placed in the third interspace 3 to 5 cm anterior to the anterior axillary line, the right arm in the fifth or sixth interspace at the anterior axillary line, and the atrial retractor arm in the fourth or fifth interspace in the midclavicular line (Fig. 36-8).

Cardiopulmonary bypass is established after cannulation of the femoral artery and vein, and venous drainage is occasionally augmented by a superior vena caval cannula introduced via the right internal jugular vein. As with a standard thoracotomy approach, aortic occlusion is achieved with a transthoracic clamp or the endoaortic balloon; the endoaortic balloon is preferred in patients with normal ascending aorta caliber (less than 3.7 cm in diameter). Myocardial protection includes antegrade cardioplegia, retrograde cardioplegia (via a percutaneous coronary sinus catheter), and moderate systemic hypothermia (cooling to 30° C).

## Partial Sternotomy

Although there was great initial enthusiasm for the partial sternotomy approach to mitral valve repair, this has recently been supplanted by interest in right-sided incisions that do not involve division of the sternum. The mitral valve can be approached via a 6- to 8-cm midline skin incision followed by either an upper or lower partial sternotomy (Fig. 36-9). With both approaches, central arterial cannulation and direct aortic cross-clamping are employed, making this the minimally invasive approach of choice in patients with small femoral arteries or peripheral arterial disease. With an upper sternotomy, venous drainage is achieved via separate cannulation of the superior and inferior vena cavae, while femoral venous cannulation is used with a partial lower sternotomy. Antegrade cardioplegia is delivered via a catheter placed directly in the ascending aorta. Mitral valve exposure with a partial upper sternotomy is obtained through an extended transseptal incision. When a partial lower sternotomy is used, the mitral valve can be exposed via a standard left atriotomy or transseptal approach. With a partial sternotomy approach, standard instrumentation is used for the repair, and sutures are tied by hand.

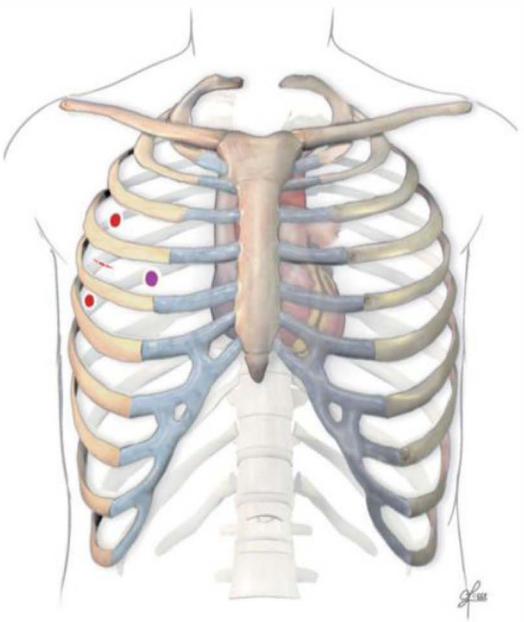


**FIGURE 36-8** Robotically assisted right-sided approach. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.)

## MITRAL VALVE REPAIR—RESULTS

Repair durability, as measured by freedom from reoperation and recurrence of MR, is excellent. Mitral valve repair for degenerative disease is associated with an operative risk of less than 1 percent. Excellent long-term survival rates have been reported, with 10-, 15-, and 20-year survival rates of 92, 76, and 48 percent, respectively. The best results are achieved with early operation, before the onset of symptoms or change in cardiac structure or function.[14,15] Standard techniques that

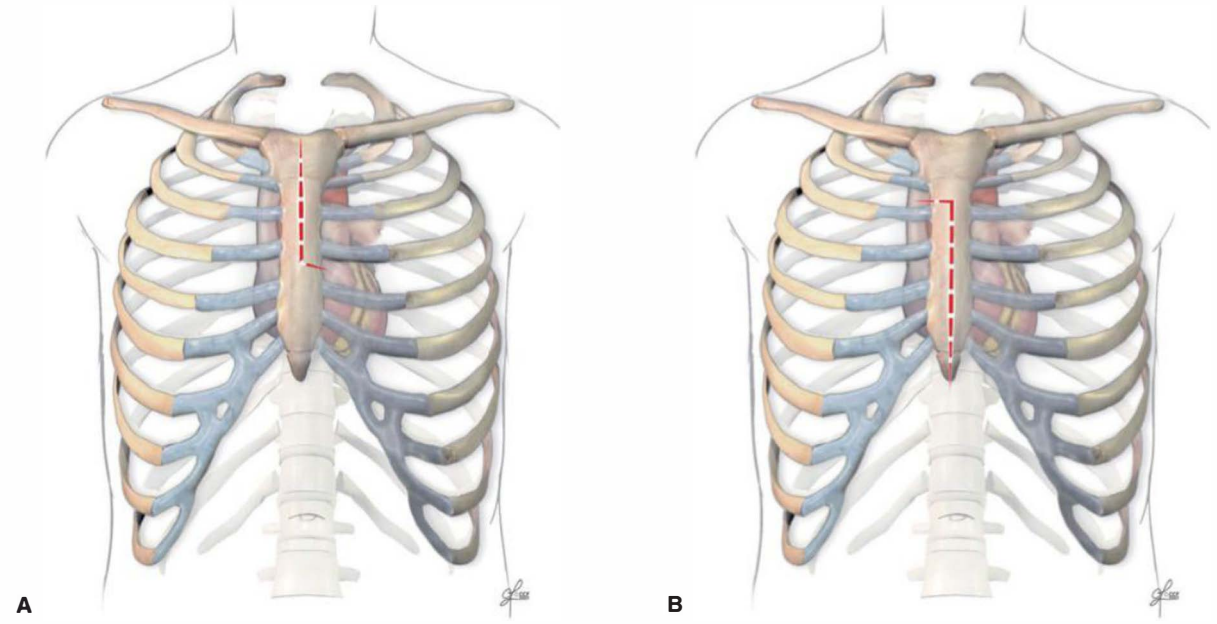



**FIGURE 36-9** **A.** Partial upper sternotomy. **B.** Partial lower sternotomy. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2010. All Rights Reserved.)

include both leaflet repair and prosthetic annuloplasty are necessary to achieve these results. Some have reported less satisfactory outcomes, with higher hospital mortality and lower repair durability.[16] This emphasizes the importance of referring patients with degenerative disease to centers of excellence. Mitral valve repair accomplished with standard techniques is highly effective and reproducible.

## SUMMARY

The key to successful mitral valve repair is to apply appropriate repair techniques. Intraoperative transesophageal echocardiography will identify the site(s) of prolapse and assist with planning. The surgical approach (sternotomy vs a minimally invasive technique) should be determined based upon preoperative testing. When repairing the valve, it is wise to keep it simple; target the pathology identified by the echocardiogram and confirmed by direct inspection. Use standard, reproducible repair techniques. And always assess the result by echocardiography; do not leave the operating room with SAM or MR that is more than mild.

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## MITRAL VALVE REPAIR FOR DEGENERATIVE DISEASE BOARD REVIEW QUESTIONS (CHAPTER 36)

1. The sliding repair technique for mitral repair was developed to:
   A. Avoid the creation of mitral stenosis with the repair
   B. Reduce the risk of postrepair systolic anterior motion
   C. Increase the area of the zone of leaflet coaptation
   D. Increase the long-term durability of the repair
   E. Obviate the need for placement of an annuloplasty band

2. An important advantage of the triangular resection technique over the quadrangular resection technique for mitral repair is:
   A. A higher success rate of repair
   B. More consistent anatomic landmarks for resection
   C. Reduction in the risk of incurring systolic anterior motion
   D. Obviates the need for annular plication sutures
   E. Can be performed for Barlow's pathology

3. One of the most important things to avoid in using artificial chordae for mitral repair is:
   A. Placing too many artificial chordae
   B. Spacing the artificial chordae too far apart
   C. Avoiding excessive tension at tying the artificial chordae
   D. Attaching the chordae too close to the free edge of the prolapsing leaflet
   E. Not using pledgets to affix the chordae to the papillary muscle tips

4. Which of the following is not a contraindication for performing a mitral repair through a right mini-thoracotomy?
   A. Patients with small femoral vessels (<7 mm)
   B. Moderate-to-severe aortic insufficiency
   C. Pectus excavatum
   D. Significant iliofemoral arterial atherosclerotic disease
   E. Obesity

5. The best clinical outcomes after mitral repair are achieved with:
   A. Early operation, before the onset of symptoms or significant change in cardiac structure or function
   B. Minimally invasive approaches
   C. Use of reduction annuloplasty alone
   D. Full sternotomy approach
   E. Using the largest annuloplasty band permissible

## ANSWERS

1. **Answer: B.** The sliding repair technique, or so-called "sliding-plasty," was developed to avoid excessive height of the posterior leaflet after resective repair. Excessive posterior leaflet height can protrude into the left ventricular outflow tract, creating a partial obstruction. This technique does not directly impact the mitral orifice area, the zone of coaptation, or durability of the repair. Placement of an annuloplasty band is recommended for virtually all types of mitral repair and is not obviated with the sliding repair technique.

2. **Answer: D.** One of the triangular resection technique's advantages over the quadrangular resection method in treating posterior leaflet prolapse is eliminating the need to place posterior annular plication sutures. Since the triangular resection does not leave a gap along the annulus, this annulus does not need to be plicated as with a posterior quadrangular resection. The triangular resection technique is not associated with a higher success rate for repair, nor does it reduce the risk for incurring systolic anterior motion. The anatomic landmarks for resection are similar to that for quadrangular resection. Both the quadrangular and triangular techniques can be used for Barlow's pathology.

3. **Answer: C.** An important technical pitfall to avoid in the use of artificial chordae is to avoid tying the chordae too tightly, leading to chordae that are too short and a restricted leaflet. The number and spacing of the chordae are not critical considerations, so long as they are of the proper length. The chordae should be placed at the free edge of the leaflet. The use of pledgets to reinforce the chordae attachment to the papillary muscle tips is variable.

4. **Answer: E.** Contraindications for performing a mitral repair through a right mini-thoracotomy include small femoral vessel caliber and significant iliofemoral artery disease, since femoral arterial cannulation is required with this approach. Moderate-to-severe aortic insufficiency is also a contraindication since antegrade cardioplegia is the primary mode of arrest with this technique. Significant pectus excavatum presents significant difficulty in obtaining adequate exposure with this intercostal approach. Although obesity can present challenges with exposure, it is not a strong contraindication for this approach.

5. **Answer: A.** The best clinical outcomes after mitral repair are associated with early operation, before the onset of symptoms or significant change in cardiac structure or function. Although minimally invasive approaches appear to confer advantages in early postoperative recovery, long-term outcome advantages have not been established conclusively with either less-invasive or full sternotomy approaches. The use of reduction annuloplasty alone is generally not adequate for posterior or anterior leaflet prolapse. Using the largest annuloplasty band permissible in all types of repairs is not advised; using the most appropriately sized band to address the pathology is recommended.

# 37

# Tricuspid Valve Disease

*David L. Joyce*

## KEY CONCEPTS

- Epidemiology
  - Although as many as 70 percent of Americans may have a small amount of tricuspid regurgitation (TR) on echocardiogram, true disease of the tricuspid valve only affects 0.8 percent of the population. Approximately 8000 surgical procedures are performed for tricuspid disease each year in the United States. The most common manifestation of tricuspid valve disease is functional TR, which occurs secondary to left-sided heart valve disease and is present in approximately 30 percent of patients with severe mitral regurgitation and up to 53 percent of patients undergoing mitral valve surgery. Risk factors for TR include age (OR 1.5/9.9 years; 95 percent CI 1.3–1.7), body mass index (OR 0.7/4.3 kg/m$^2$; 95 percent CI 0.6–0.8), and female gender (OR 1.2; 95 percent CI 1.0–1.6).
- Pathophysiology
  - In most cases, tricuspid valve disease presents as functional regurgitation secondary to left-sided valvular disease or heart failure (particularly in the setting of pulmonary hypertension). Structural causes of tricuspid valve disease are less common, and include rheumatic heart disease, endocarditis, carcinoid, papillary muscle dysfunction, trauma (often from endomyocardial biopsies or pacemaker lead placement), and congenital anomalies.
- Clinical features
  - Tricuspid valve disease is often detected incidentally during evaluation for left heart conditions. Signs and symptoms are often consistent with congestive heart failure and can include dyspnea on exertion, orthopnea, jugular venous distention, ascites, and peripheral edema. Advanced disease also can present with hemoptysis and paroxysmal nocturnal dyspnea. Physical examination reveals a pansystolic (TR) or presystolic [tricuspid stenosis (TS)] murmur in the fourth and fifth intercostal spaces at the left sternal border or epigastrium. Hepatojugular reflux, pulsatile liver, and signs of hepatic dysfunction also may be present. Tricuspid endocarditis often presents with pneumonia or manifestations of septic emboli.
- Diagnostics
  - Electrocardiographic features include peaked P waves or a Q wave in V1 as a result of right atrial volume overload and enlargement. Plain chest radiography may demonstrate cardiomegaly with right-sided chamber enlargement. Doppler and two-dimensional echocardiography confirm the diagnosis, revealing structural abnormalities and measuring pulmonary arterial pressures, degree of stenosis/regurgitation, and right ventricular dysfunction. Cardiac catheterization usually confirms elevated right atrial and ventricular end-diastolic pressures in TR. A diastolic pressure–atrioventricular pressure gradient that increases with respiration is found in patients with significant TS. Tricuspid endocarditis is typically diagnosed in the setting of major criteria that include valvular vegetations and pyrexia; positive blood cultures, septic pulmonary emboli, and a murmur constitute the minor criteria.
- Treatment
  - Tricuspid valve repair or replacement is indicated for TS and moderate-to-severe TR, usually associated with New York Heart Association class III or IV symptoms. TS is usually treated with commissurotomy.
  - Surgical techniques for TR include bicuspidization, DeVega suture annuloplasty, Carpentier ring annuloplasty, and prosthetic valve replacement.
- Outcomes
  - Untreated, the 1-year survival in patients with severe, moderate, mild, and absent TR is approximately 60, 70, 90, and 91 percent, respectively. The DeVega suture annuloplasty for TR is associated with a 4 percent operative mortality, a 5 percent recurrence rate, and an actuarial survival rate of 71.5 percent at 14 years. Carpentier ring annuloplasty is associated with an actuarial survival of 68.3 percent at 10 years.

# INTRODUCTION

## Definitions

Diseases of the tricuspid valve can be subdivided in several ways. The broadest distinction separates congenital lesions (e.g., Ebstein's anomaly, tricuspid atresia) from those which are acquired. This chapter focuses primarily on acquired lesions, which can be divided into functional (secondary) disease and organic (primary) disease. Functional disease typically occurs in the setting of an anatomically normal valve and results from pulmonary artery hypertension and right ventricular (RV) dilatation. This condition most often is secondary to left-sided valvular disease but also may result from Eisenmenger's syndrome, RV infarction, or primary pulmonary hypertension (PPH). These types of disease typically manifest in the clinical presentation of tricuspid regurgitation (TR). Organic disease (in which there is a structural abnormality of the valve) is associated most frequently with rheumatic fever but also may occur in the setting of congenital anomalies, infective endocarditis, radiation therapy, trauma (from endomyocardial biopsies or pacemaker lead insertion), carcinoid syndrome, Libman–Sacks endocarditis, eosinophilic leukemia, and diffuse collagen disorders. Tricuspid stenosis (TS) is often present in organic disease, although insufficiency can occur alone or in combination with stenosis. A summary of the disorders implicated in tricuspid valve regurgitation is given in Figure 37-1.

## Historic Highlights

Starr and colleagues[1] reported the first surgical experience with tricuspid valve replacement (TVR) in a series of 13 patients who had undergone multiple valve replacement; one of those patients underwent replacement of the aortic, mitral, and tricuspid valves on February 21, 1963. Although the paucity of indications for TVR limited its implementation, the recognition of tricuspid valve endocarditis as an epidemic among heroin addicts in Detroit between 1966 and 1968 rejuvenated interest in tricuspid valve surgery. Valve

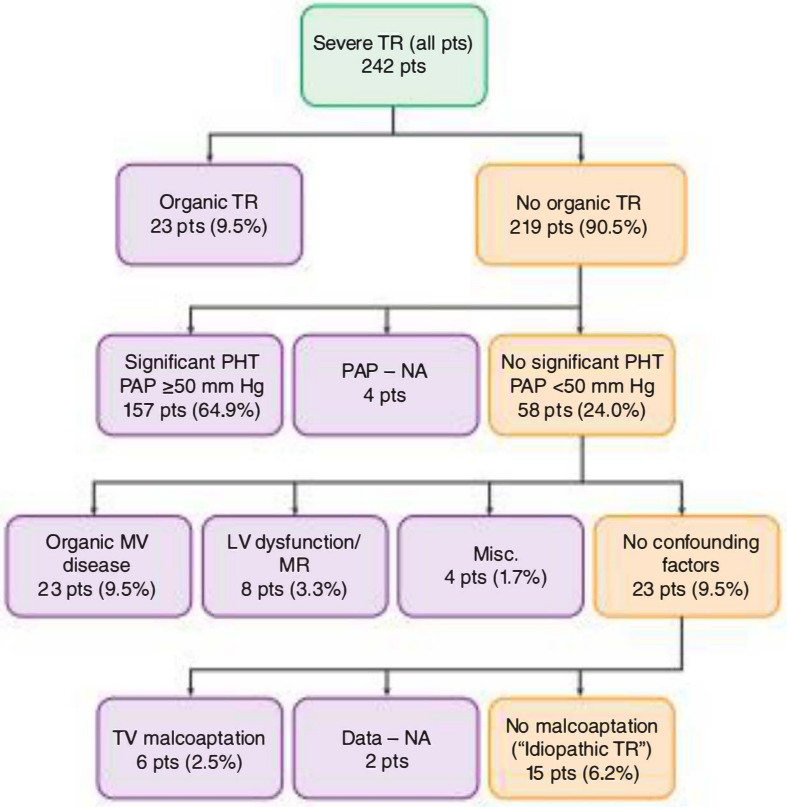



**FIGURE 37-1** Distribution of causes for patients with severe tricuspid regurgitation (TR). LV, Left ventricular; misc, miscellaneous; MR, mitral regurgitation; MV, mitral valve; NA, data not available; PAP, pulmonary artery pressure (systolic); PHT, pulmonary hypertension; pts, patients; TV, tricuspid valve; bold arrows, criteria for definition of idiopathic TR. (Reproduced with permission from Mutlak D, Lessick J, Reisner SA, Aronson D, Dabbah S, Agmon Y (eds). Echocardiography-based spectrum of severe tricuspid regurgitation: The frequency of apparently idiopathic tricuspid regurgitation. *J Am Soc Echocardiogr* 2007 Apr;20(4):405–408. Copyright Elsevier.)

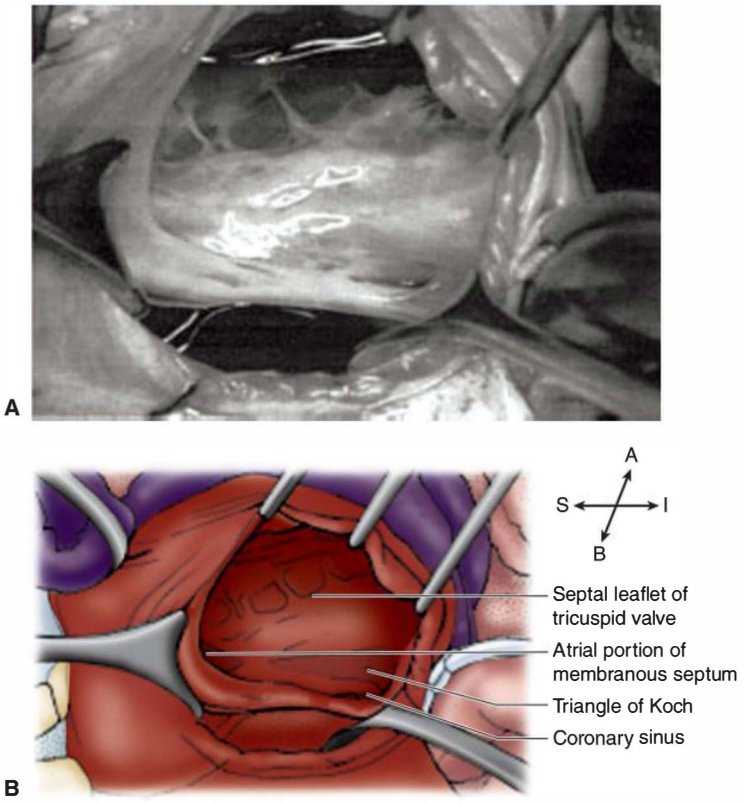



**FIGURE 37-2** Anatomic features of the normal tricuspid valve. (With permission from Cohn LH, Edmunds LH Jr (eds). *Cardiac Surgery in the Adult*. New York: McGraw-Hill, 2003:1001–1015.)

replacement combined with intravenous antibiotics failed to control severe gram-negative sepsis, yielding a mortality rate of 100 percent. In search of a more efficacious treatment strategy, Agustin Arbulu began performing experimental removal of the tricuspid valve. After demonstrating the efficacy of this technique in a canine model, Arbulu removed the tricuspid valve in 55 patients with tricuspid endocarditis secondary to *Pseudomonas aeruginosa* with a 61 percent survival rate at 25 years.[2,3]

## Anatomic Considerations

The tricuspid valve complex contains the following structures (Fig. 37-2)[4]:

- Three leaflets (anterior, posterior, and septal)
- The chordate tendinae
- Two papillary muscles
  - The anterior papillary muscle gives chordae to the anterior and posterior leaflets.
  - The medial papillary muscle gives chordae to the posterior and septal leaflets.
- The fibrous tricuspid annulus
- The right atrial and RV myocardium.

The adult valve is typically 36 ± 4.5 mm in diameter and covers a surface area of 10.5 $cm^2$. In the setting of dilated cardiomyopathy, the valve diameter can increase to 45 mm in some cases. Important anatomic considerations for the surgeon include the presence of the atrioventricular node (AVN) and conducting system within the triangle of Koch demarcated as the base of the septal leaflet, coronary sinus orifice, and tendon of Todaro. The relationships of the annulus to the base of the aortic valve, the membranous septum, the central fibrous body, the right coronary artery, and the lateral atrioventricular junction are also important.

# PATHOPHYSIOLOGY

Disorders of the tricuspid valve can result from structural abnormalities or changes in ventricular geometry in the setting of a normal valve. TS is due to rheumatic heart disease in over 90 percent of cases.[4] Conversely, pure TR is usually a consequence of RV dilatation and failure.

## Tricuspid Stenosis

The surgical pathology of TS can be divided into four categories: rheumatic disease, congenital anomalies, metabolic

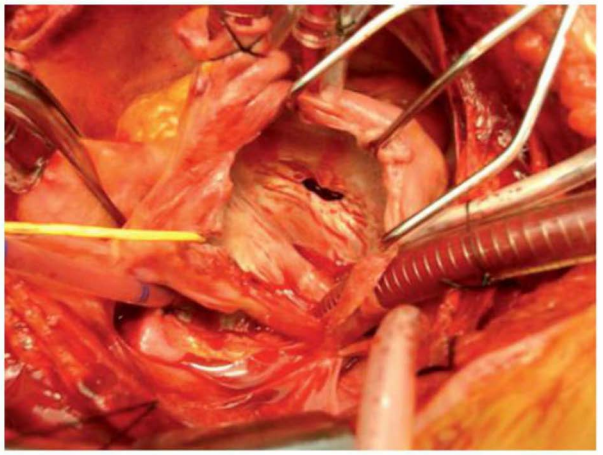


FIGURE 37-3 Surgical finding of a stenotic tricuspid valve secondary to rheumatic heart disease. (Image reprinted with permission from Medscape Reference (http://emedicine.medscape.com/), 2013, available at http://emedicine.medscapte.com/article/158604-overview.)

disorders, and infective endocarditis.[5] On gross pathology, stenotic tricuspid valves are found to have fibrous thickening of the leaflets with shortening and thickening of the chordae tendineae. Fusion of the commissures leads to obstruction of blood flow and the resultant symptoms of TS (Fig. 37-3). Histologic examination of the valvular tissue reveals deposition of collagen and elastic fibers.[5]

## Tricuspid Regurgitation

Regurgitation of the tricuspid valve results from a wide array of entities. Worldwide, the most common causes of TR include rheumatic heart disease and endocarditis.[6] Other less common causes of organic TR include carcinoid, papillary muscle dysfunction, trauma, connective tissue disorders, rheumatoid arthritis, and radiation therapy.[7] In North America, functional TR is more prevalent secondary to annular dilatation and the sequelae of left-sided valvular disease and pulmonary hypertension.[6] Gross pathologic features of the regurgitant tricuspid valve include fibrous thickening of the leaflets, minimal calcification, and dilatation of the annulus.[7] In contrast to TS, there is no fusion of the commissures or shortening of the chordae.

# CLINICAL FEATURES

## Epidemiology

Tricuspid valve disease affects 0.8 percent of Americans, making it a much rarer condition than diseases of the mitral valve, which affect 2.4 percent and 1.6 percent of the general population.[8] Although most patients with tricuspid disease are treated medically, approximately 8000 surgical procedures are performed for tricuspid disease each year in the United States.[8] The most common manifestation of tricuspid valve disease is functional TR, which occurs secondary to left-sided heart valve disease and is present in approximately 30 percent of patients with severe mitral regurgitation and up to 53 percent of patients undergoing mitral valve surgery.[8] Internationally, tricuspid valve disease is more common due to the increased prevalence of rheumatic heart disease. In Latin America and India, this condition affects 4 out of every 100,000 people. In the Framingham Heart Study, the determinants of TR were age (OR 1.5/9.9 years; 95 percent CI 1.3–1.7), body mass index (OR 0.7/4.3 kg/m$^2$; 95 percent CI 0.6–0.8), and female gender (OR 1.2; 95 percent CI 1.0–1.6).[9]

## History and Physical Examination

Signs and symptoms of tricuspid valve disease are illustrated in Table 37-1.[10] Tricuspid valve disease usually is brought to the attention of the medical practitioner during evaluation of left-sided conditions. A history of rheumatic heart disease or an abnormality detected on cardiac auscultation may alert the clinician, but frequently these patients present with dyspnea on exertion, orthopnea, and other symptoms of left-sided failure. In advanced cases, hemoptysis and paroxysmal nocturnal dyspnea may occur.[11]

Signs of tricuspid valve disease are related to the onset of right heart failure and include jugular venous distention, ascites, and peripheral edema. Patients also may complain of vague abdominal discomfort associated with hepatomegaly. In light of the high rate of concordant left-sided disease, most patients are detected on the basis of congestive heart failure. Physical examination is notable for the presence of a murmur, which can be auscultated

**TABLE 37-1: Signs and Symptoms of Tricuspid Valve Disease**

| |
|---|
| **Symptoms** |
| Fatigue |
| Liver/gut congestion |
| Right upper quadrant discomfort |
| Dyspepsia |
| Indigestion |
| Fluid retention with leg edema |
| Ascites |
| **Physical signs** |
| Stenosis: low-to-medium-pitch diastolic rumble with inspiratory accentuation |
| Regurgitation: soft, early, or holosystolic murmur augmented with inspiratory effort (Caravallo's sign) |
| Prolapse: systolic honk |

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at the left sternal edge at the fourth and fifth intercostal spaces or in the epigastrium. The murmur of TR is pansystolic and may be high-pitched, often increasing on inspiration (Carvallo's sign). TS produces a presystolic murmur that also increases with inspiration. This feature permits its differentiation from murmurs associated with mitral valve disease. An S3 may be appreciated in cases of ventricular dilatation, while an S4 may indicate a hypertrophied ventricle. Atrial fibrillation is a common finding. Hepatojugular reflux or a pulsatile liver may be demonstrated in cases of TR, and clinical signs of hepatic dysfunction also may be present.

## DIAGNOSTIC MODALITIES

In 2006, the American College of Cardiology (ACC) and American Heart Association (AHA) introduced guidelines for the evaluation of TR in adolescents and young adults.[12] These recommendations are summarized in Table 37-2. Routine laboratory tests may aid in the diagnosis of the underlying condition, with leukocytosis commonly seen in the setting of infective endocarditis. Renal and hepatic impairment also may be present in cases of chronic ventricular dysfunction.

**TABLE 37-2: ACC/AHA Guidelines for Evaluation of Tricuspid Regurgitation (TR) in Adolescents and Young Adults**

**Class I—There is evidence and/or general agreement that the following tests should be obtained in adolescents and young adults with TR**

Electrocardiogram at the initial evaluation and serially every 1 to 3 years, depending upon severity

Chest radiograph at the initial evaluation and serially every 1 to 3 years, depending upon severity

Doppler echocardiography at the initial evaluation and serially every 1 to 3 years, depending upon severity

If an atrial communication is present, pulse oximetry at rest and/or during exercise at the initial evaluation and serially every 1 to 3 years, depending upon severity

**Class IIa—The weight of evidence or opinion is in favor of the usefulness of the following tests in adolescents and young adults with TR**

Electrophysiology study for symptomatic atrial arrhythmias

Exercise testing at the initial evaluation and serially every 1 to 3 years

**Class IIb—The weight of evidence or opinion is less well established for the usefulness of the following tests in adolescents and young adults with TR**

Among asymptomatic patients, Holter monitoring at the initial evaluation and serially every 1 to 3 years

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Electrocardiographic findings include peaked P waves (caused by right atrial overload) or a Q wave in $V_1$ (resulting from an enlarged right atrium). Posteroanterior and lateral plain chest radiography may demonstrate cardiomegaly with enlargement of the right-sided cardiac structures. A pleural effusion also may be present along with upward displacement of the diaphragm resulting from ascites. Echocardiography represents the mainstay of diagnostic evaluation, with color flow mapping used in two orthogonal planes to estimate severity by analysis of vena contracta width, flow convergence calculations, and evaluating the direction and size of the jet.[4] Specific echocardiographic criteria for severe TR include vena contracta width greater than 0.7 cm, Proximal Isovelocity Surface Area (PISA) radius greater than 0.9 cm (at Nyquist limit of 50–60 cm/s), systolic flow reversal in the hepatic veins, and dilatation of the RV, right atrium, and inferior vena cava.[8] Structural abnormalities of the valve can be demonstrated along with measurement of pulmonary artery pressures and RV function. Interpretation of echocardiographic findings of TR must be taken in the context of the patient's clinical condition, since severity can be influenced by dynamic properties such as volume status and afterload.[4]

Right heart catheterization provides useful information for evaluating the anatomy and functionality of the tricuspid valve. In the setting of TR, right atrial and ventricular end-diastolic pressures usually are elevated. TS is characterized by a diastolic pressure gradient between the right atrium and the right ventricle that increases during inspiration and decreases with expiration. Contrast right ventriculography is rarely needed in the workup of tricuspid valve disease due to the abundance of useful information that can be gained from transthoracic echocardiography. In older patients and those with risk factors for coronary artery disease, a left heart catheterization may be required to document the status of the coronary circulation.

## MEDICAL THERAPY

Acquired disease of the tricuspid valve represents a structural abnormality for which there is no effective pharmacotherapy. In general, tricuspid insufficiency is well tolerated in the absence of elevated pulmonary pressures. For example, echocardiograms performed in 95 healthy women revealed some degree of TR in 52 subjects.[13] Medical therapy is directed toward addressing the underlying cause of pulmonary hypertension, such as treating chronic obstructive pulmonary disease (COPD). Diuretics may be effective in reducing peripheral edema and hepatic congestion. Nevertheless, elevation of the pulmonary vascular resistance may dictate surgical repair in selected patients. TS has been treated with balloon valvotomy in several small series. However, there are no published studies that compare balloon valvotomy with surgical valvuloplasty. In addition, severe TR is a common complication of balloon valvotomy.

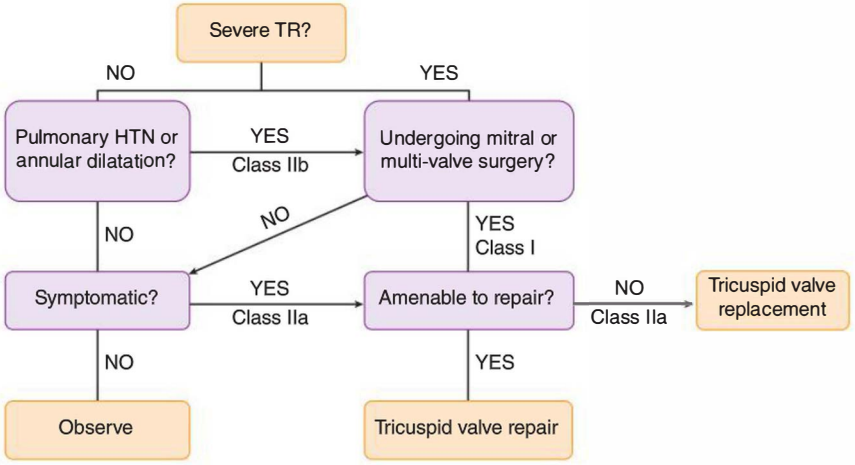



**FIGURE 37-4** Flow diagram for the management of tricuspid regurgitation.

# SURGICAL THERAPY

## Surgical Decision Making

A flow diagram for surgical decision making is provided in Figure 37-4. In addition, ACC/AHA guidelines are reviewed in Table 37-3. Tricuspid valve repair is indicated in patients with severe TR who are undergoing mitral valve surgery or multiple valve surgery.[12] It is reasonable to consider tricuspid valve repair or replacement in cases of severe symptomatic primary TR as well as in mild TR in patients undergoing mitral valve surgery in the setting of pulmonary hypertension or tricuspid annular dilatation.[12] Tricuspid valve surgery should not be considered in patients with mild primary TR or those who are asymptomatic with a normal mitral valve and pulmonary artery systolic pressures of less than 60 mm Hg.[12]

## Operative Techniques

Surgical management of acquired diseases of the tricuspid valve has evolved from reparative techniques to prosthetic replacement and back again after greater experience with and modifications of each of those techniques. Since operative repair of tricuspid valve lesions is performed most commonly in the setting of concomitant cardiac surgical procedures, median sternotomy is typically the approach of choice.

### TRICUSPID STENOSIS: COMMISSUROTOMY

For TS that is not amenable to balloon valvuloplasty, surgical management is straightforward and involves commissurotomy of the diseased valve. Successful commissurotomy requires adequate visualization of the valve and careful attention to the surrounding anatomic structures.[14] It is usually unnecessary to open all three commissures, since such maneuvers are likely to result in significant tricuspid insufficiency that is difficult to correct. Instead, separation of the fused commissures on either side of the septal leaflet results in a

**TABLE 37-3: ACC/AHA Guidelines for Surgical Management of Tricuspid Valve Disease**

**Class I**

Tricuspid valve repair is beneficial for severe TR in patients with MV disease requiring MV surgery
(Level of Evidence: B)

**Class IIa**

1. Tricuspid valve replacement or annuloplasty is reasonable for severe primary TR when symptomatic
(Level of Evidence: C)
2. Tricuspid valve replacement is reasonable for severe TR secondary to diseased/abnormal tricuspid valve leaflets not amenable to annuloplasty or repair
(Level of Evidence: C)

**Class IIb**

Tricuspid annuloplasty may be considered for less than severe TR in patients undergoing MV surgery when there is pulmonary hypertension or tricuspid annular dilatation
(Level of Evidence: C)

**Class III**

1. Tricuspid valve replacement or annuloplasty is not indicated in asymptomatic patients with TR whose pulmonary artery systolic pressure is less than 60 mm Hg in the presence of a normal MV
(Level of Evidence: C)
2. Tricuspid valve replacement or annuloplasty is not indicated in patients with mild primary TR
(Level of Evidence: C)

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straight (septal) and a curved (mural) leaflet with excellent hemodynamic properties.[15]

## TRICUSPID REGURGITATION

Surgical techniques for addressing TR include bicuspidization, purse-string (DeVega) reduction of the annulus, placement of rigid or flexible annuloplasty (Carpentier) rings, and prosthetic replacement. Selection of the appropriate treatment depends on the extent of dysfunction and the condition of the native valve. The goals of therapy include restoration of normal valve function through the use of an easily reproducible technique that yields consistent results.[16]

***Bicuspidization.*** The posterior annulus of the tricuspid valve is the only structurally unsupported area of the tricuspid valve annulus, making this area particularly susceptible to dilatation and subsequent TR.[16] Various annuloplasty techniques have been described that are based on the principle of correcting this abnormality.[6] Bicuspidization for tricuspid insufficiency is performed using one or two pledgeted polypropylene sutures to obliterate the annular segment corresponding to the posterior leaflet. This technique is generally satisfactory in patients with moderate TR. In a similar technique, an edge-to-edge repair can be used to reduce the size of the regurgitant annulus.

***DeVega Suture Annuloplasty.*** Owing to its simplicity, the DeVega repair has gained popularity for the management of moderate-to-severe TR. This technique involves running a single pledgeted polypropylene suture between the anterior and septal leaflets at the level of the commissure.[6] Two sequential sutures are placed in this fashion, running clockwise through the annulus. These sutures are tightened to obliterate the portion of the annulus that has been plicated (Fig. 37-5). On the basis of some estimates, up to 26 percent of patients undergoing surgery of the mitral or aortic valve may require tricuspid annuloplasty.[17] Operative mortality after DeVega annuloplasty is around 4 percent.[18] Recurrence of tricuspid insufficiency has been demonstrated in 5 percent of patients undergoing this procedure and has been attributed to an inadequate mitral valve procedure or left ventricular failure.[19] Long-term follow-up of this procedure shows an actuarial survival rate of 71.5 ± 8.2 percent at 14 years.[20]

***Carpentier Ring Annuloplasty.*** In cases of severe TR, rigid or flexible ring annuloplasty is well accepted as optimal therapy. The principles of repair are similar to those for suture annuloplasty with respect to reducing the size of the valve orifice. However, the increase in dilatation seen in cases of severe TR mandates greater stability with the repair. A sizer is used to measure the area of the septal leaflet to allow selection of the appropriate ring. Tricuspid rings are designed with an opening that corresponds to the region of the AVN to minimize the chance of incurring damage to the conducting system during surgery. Interrupted pledgeted 2-0 non-absorbable sutures are placed through the annulus and then passed through the ring, securing it in place (Fig. 37-6). First described by Carpentier and colleagues,[21] this procedure has undergone several modifications. Nevertheless, the principles of repair remain the same regardless of the type of ring used. This technique has been estimated to be suitable in up to 96 percent of cases of acquired tricuspid valve disease and is associated with a hospital mortality rate of 9 to 10 percent in patients undergoing concomitant left-sided valve surgery (nonvalve-related deaths).[22] Actuarial survival from this procedure at 10 years is 68.3 percent.[23] A recent study comparing several different suture and ring annuloplasty techniques demonstrated an increase in recurrent TR over time with the DeVega annuloplasty.[24] These findings have led to the recommendation that suture annuloplasties be abandoned in favor of various types of ring annuloplasties to reduce the rate of reoperation, which has an associated hospital mortality rate of 37 percent.[24]

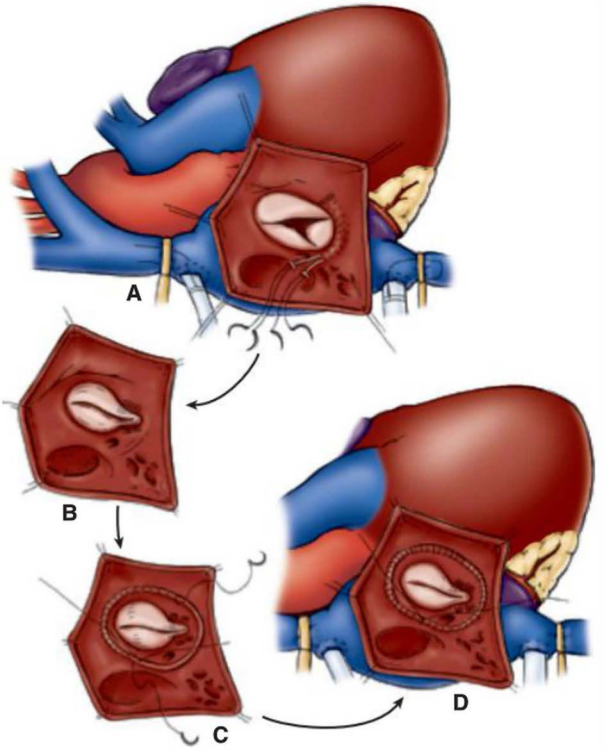



**FIGURE 37-5** A modified DeVega annuloplasty technique is shown. (Reproduced with permission from Cohn LH, Edmunds LH Jr (eds). *Cardiac Surgery in the Adult*. New York: McGraw-Hill, 2003:1001–1015.)

## TRICUSPID VALVE REPLACEMENT

After tricuspid valve repair, assessment of persistent insufficiency can be determined by one or more of the following techniques: (1) injection of saline into the right ventricle with a clamp occluding the pulmonary artery; (2) manual palpation

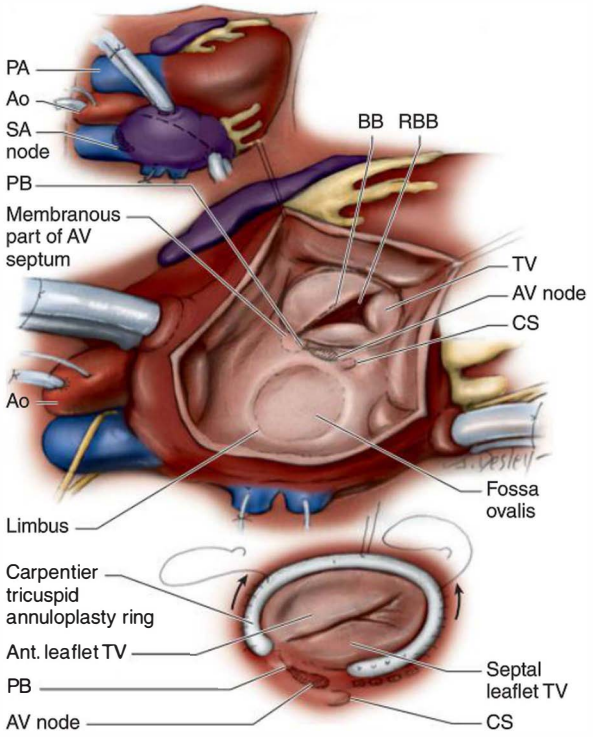



**FIGURE 37-6** Technique for tricuspid annuloplasty using a Carpentier–Edwards ring. PA, pulmonary artery; Ao, aorta; SA, sinoatrial; PB, penetrating bundle; AV, atrioventricular; TV, tricuspid valve; CS, coronary sinus; RBB, right bundle branch; BB, bundle branch. (Reproduced with permission from Kirklin JW, Barratt-Boyer BG. *Cardiac Surgery*, 2nd ed. New York: Churchill Livingstone, 1993:592.)

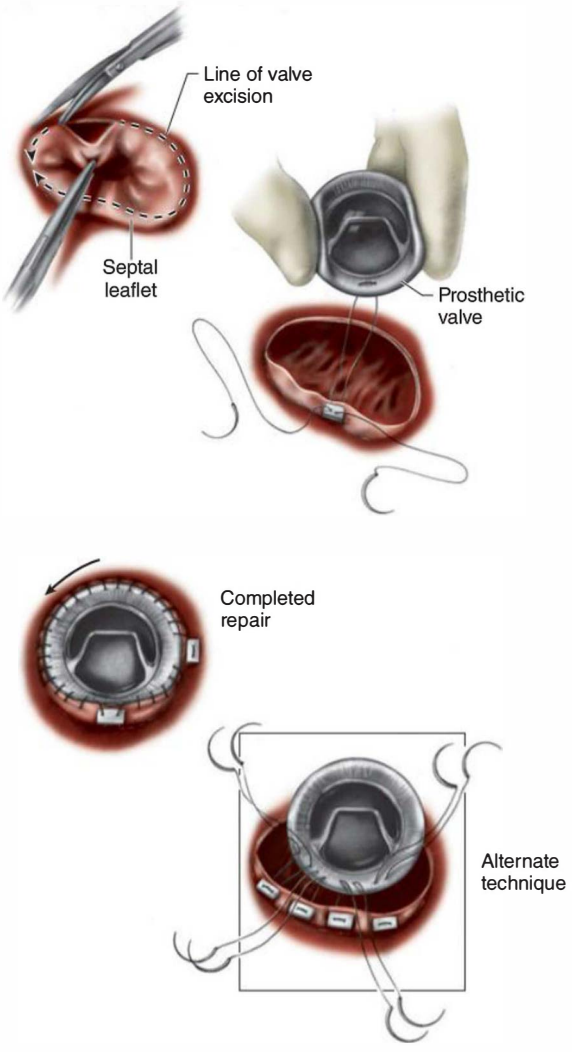



**FIGURE 37-7** Technique for tricuspid valve replacement. (Reproduced with permission from Doty DB. *Cardiac Surgery: Operative Technique*. St. Louis: Mosby, 1997.)

for regurgitant flow performed by inserting a finger through the right atrial appendage; and (3) transesophageal echocardiography. Valve replacement should be performed in cases of persistent tricuspid insufficiency or in instances where the valve morphology is not suitable for repair at the time of initial inspection. Predictors for the need for valve replacement include jugular venous distention, increased severity of tricuspid valve incompetence, previous cardiac surgery, and the presence of TS.[25] Because of the increased rate of thromboembolism and valve thrombosis associated with mechanical valve replacement, tissue valves are preferred in most cases. In a meta-analysis of 1160 prosthetic valves, the pooled survival hazard ratio of mechanical prosthesis versus bioprosthesis was found to be 1.07.[26] The freedom from reoperation hazard ratio was 1.24 in that study.[26] Survival rates have been found to be similar between the two types of valve replacement. The surgical technique involves placement of interrupted pledgeted non-absorbable imbricating sutures that are passed initially through the leading edge of the valve leaflets and subsequently through the prosthetic valve sewing ring (Fig. 37-7). Paying careful attention to the regional anatomy and leaving the native valve leaflets in place reduce the likelihood of injury to the conduction system.

## OUTCOMES/PROGNOSIS

Based on the results of a large retrospective VA study, severe TR has been found to be associated with a poor prognosis; this risk exists independent of age, biventricular systolic function, RV size, and dilation of the inferior vena cava.[27] Increase in the severity of TR has also been demonstrated to correlate with worsening survival, with 1-year survival rates of 90.7 percent with no TR, 90.3 percent with mild TR, 78.9 percent with moderate TR, and 63.9 percent with severe TR.[27] Improvement in outcomes has been consistently demonstrated with surgical correction of severe TR. In a recent study by Kim et al., operative mortality was 10 percent for isolated severe TR.[28] Factors that were associated with a poorer prognosis included preoperative anemia and

larger RV end systolic area.[28] When tricuspid valve replacement or repair is undertaken after left-sided valve surgery, the outcomes are improved with no hospital mortality and 1-, 5-, and 10-year survival of 97, 93, and 63 percent after replacement and 93, 93, and 81 percent after repair in a recent study by Park et al.[29] In this study, LV ejection fraction <40 percent and age were both found to be independent risk factors for mortality.[29] Although tricuspid valve repair remains the procedure of choice in cases of severe TR, valve replacement represents an acceptable alternative when repair is not possible.

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## TRICUSPID VALVE DISEASE BOARD REVIEW QUESTIONS (CHAPTER 37)

1. Which structure is not associated with the triangle of Koch?
   A. Atrioventricular node
   B. Coronary sinus
   C. Septal leaflet
   D. Tendon of Todaro
   E. Right coronary artery

2. Which of the following represents one of the major Doppler criteria for severe TR?
   A. Vena contracta width >0.7 cm
   B. Annular dilation
   C. Paradoxical interventricular septal movement
   D. Hyperdynamic RV function
   E. Pulmonary hypertension

3. Which of the following is not an indication for tricuspid valve surgery?
   A. Severe TR in patients with mitral valve disease requiring mitral valve surgery
   B. Severe symptomatic primary TR
   C. Severe TR secondary to diseased/abnormal tricuspid valve leaflets
   D. Severe TR in patients undergoing mitral valve surgery when there is pulmonary hypertension or tricuspid annular dilation
   E. TR and pulmonary artery systolic pressure is less than 60 mm Hg

4. A patient requires mitral and tricuspid valve repair along with coronary artery bypass grafting to the PDA. What is the proper sequence for this operation?
   A. Mitral valve repair, tricuspid valve repair, distal coronary anastomosis, proximal anastomosis
   B. Distal coronary anastomosis, mitral valve repair, proximal anastomosis, tricuspid valve repair
   C. Distal coronary anastomosis, mitral valve repair, tricuspid valve repair, proximal anastomosis
   D. Tricuspid valve repair, mitral valve repair, distal coronary anastomosis, proximal anastomosis
   E. Mitral valve repair, distal coronary anastomosis, tricuspid valve repair, proximal anastomosis

5. Which of the following statements is true regarding surgical approach to the tricuspid valve?
   A. Jugular venous distention, increased severity of tricuspid valve incompetence, previous cardiac surgery, and the presence of TS all mandate valve replacement
   B. Mechanical valve replacement is preferred over tissue valve replacement given the high rate of complications with bioprosthetic valves
   C. Persistent leak after bicuspidization warrants valve replacement
   D. The DeVega technique is acceptable for cases of functional TR in which the loading conditions are expected to improve over time
   E. Ring annuloplasty techniques have a higher rate of endocarditis compared with alternative repair techniques

## ANSWERS

1. **Answer: E.** The right coronary artery is not associated with the triangle of Koch. The triangle of Koch is formed by the septal leaflet of the tricuspid valve, the coronary sinus, and the tendon of Todaro. The AVN is contained within this triangle.
2. **Answer: A.** Although all of these findings may be present in severe TR, major Doppler criteria include vena contracta width >0.7 cm and systolic flow reversal in the hepatic veins. Atrial fibrillation may limit the accuracy of systolic flow reversal as a finding.
3. **Answer: E.** Tricuspid valve repair is indicated in patients with severe TR who are undergoing mitral valve surgery or multiple valve surgery. It is reasonable to consider tricuspid valve repair or replacement in cases of severe symptomatic primary TR as well as in mild TR in patients undergoing mitral valve surgery in the setting of pulmonary hypertension or tricuspid annular dilatation. Tricuspid valve surgery should not be considered in patients with mild primary TR or those who are asymptomatic with a normal mitral valve and pulmonary artery systolic pressures of less than 60 mm Hg.
4. **Answer: B.** Sewing the distal anastomosis first will prevent the dreaded complication of atrioventricular separation which can occur when lifting the heart after mitral valve procedures. It also permits cardioplegia to be given through the graft during subsequent repair procedures. Tricuspid annuloplasty can be performed after removal of the cross-clamp after the heart is beating.
5. **Answer: D.** Jugular venous distention, increased severity of tricuspid valve incompetence, previous cardiac surgery, and the presence of TS all represent risk factors for failed repair. However, their presence alone does not mandate valve replacement. Bioprosthetic valves do not carry a higher complication rate and are preferred in most cases of valve replacement. Persistent regurgitation may improve after ring annuloplasty in attempted bicuspidization procedures. The DeVega technique is an appropriate option for cases of functional TR in which the loading conditions are expected to improve over time. There is no evidence that endocarditis risk increases with ring annuloplasty.

38

# Surgical Treatment of Endocarditis

*John R. Doty*
*William T. Caine*

## KEY CONCEPTS

- Epidemiology
  - The overall incidence of infective endocarditis in the general population ranges from 3 to 11 cases per 100,000 person-years. The most common underlying conditions are native valvular heart disease, previously implanted prosthetic valves and congenital heart disease. Endocarditis is more common in the elderly and males. The increasing use of indwelling intravenous catheters and leads for cardiac rhythm devices is associated with iatrogenic endocarditis.
- Pathophysiology
  - There are five distinct steps in the sequence of events resulting in endocarditis. First, there is damage to the endocardial surface of the valve or other cardiac structure. Second, there is the accumulation of thrombus and platelets on the damaged surface, termed nonbacterial thrombotic endocarditis (NBTE). Third, the patient develops a transient blood stream infection, usually bacteremia. Fourth, there is deposition and adherence of infectious organisms on the focus of NBTE. Fifth, the organisms grow and multiply at the NBTE site.
- Clinical Features
  - The clinical presentation of endocarditis depends upon the rapidity of onset, the virulence of the underlying organism, and the coexistence of underlying cardiac disease. Patients with acute endocarditis usually present early in the infection with substantial illness. Complications are common and are due to embolism and valvular destruction. Such complications include brain embolism, intracranial hemorrhage, heart failure, myocardial infarction, and peripheral embolism.
- Diagnostics
  - Physical examination, blood cultures and echocardiography are the cornerstones for the diagnosis of endocarditis. Adherence to the major and minor criteria of the modified Duke classification guide diagnosis and subsequent management. Transthoracic echocardiography is usually sufficient to identify the vegetation, but transesophageal provides the optimal method for establishment of endocarditis according to the Duke major criteria.
- Treatment
  - Prompt and accurate antimicrobial therapy should be initiated for the patient with endocarditis. In general, antibiotic therapy will be administered intravenously in high dosages for a prolonged period of time. The primary goals of operation for endocarditis are removal of all infected tissue and correction of the hemodynamic abnormality. Infection of a cardiac valve necessitates either repair or replacement.
- Outcome
  - Mortality after operation for endocarditis ranges widely, with reports of hospital death between 4 and 30 percent. In general, operative mortality is affected by the urgency of the operation, concomitant preoperative heart failure, nonstreptococcal organisms, and prosthetic valve endocarditis. Neurologic deficits can be worsened if surgery is performed within the first few weeks after the initial event. Recurrent endocarditis is uncommon (2–5 percent) if all infected tissue has been removed and there is no active infection at the time of operation.

## INTRODUCTION

Infective endocarditis (IE) is defined as any condition in which an infective process has affected a structure of the heart. The valves are the most common location for endocarditis, but the process may also involve atrial or ventricular septal defects, patent ductus arteriosus, or any of a wide range of congenital heart defects, including the aorta and great vessels. Depending on the involved area, the infective process can lead to progressive valvular dysfunction, systemic embolization, congestive heart failure, fistula formation, conduction abnormalities, and other organ dysfunction.

The presentation of IE includes acute, subacute, and chronic forms. In addition, the process can involve either the native structures of the heart or previously placed prostheses, such as valves or shunts. Organisms that cause endocarditis include bacteria, viruses, and fungi. Demonstration of both the organism and the sequelae of infection on cardiovascular function is essential for proper treatment.

The knowledge of established treatment guidelines for IE as well as the long-term sequelae of medically managed endocarditis is important for correct surgical therapy. Osler described the classical findings of endocarditis in 1885, and later stressed the importance of blood cultures for diagnosis.[1,2] Kay and colleagues were the first to describe successful surgical treatment of endocarditis in 1961, performing debridement of an infected tricuspid valve and simultaneous closure of a ventricular septal defect.[3] Wallace and colleagues performed the first valve replacement for aortic valve endocarditis in 1965.[4]

## PATHOGENESIS

There are five distinct steps in the sequence of events resulting in endocarditis. First, there is damage to the endocardial surface of the valve or other cardiac structure. Second, there is the accumulation of thrombus and platelets on the damaged surface, termed nonbacterial thrombotic endocarditis (NBTE). Third, the patient develops a transient blood stream infection, usually bacteremia. Fourth, there is deposition and adherence of infectious organisms on the focus of NBTE. Fifth, the organisms grow and multiply at the NBTE site.

### Damage to the Endocardial Surface

The endocardial surface may become damaged from one of several methods. Congenitally malformed valves or anomalous flow pathways, such as a ventricular septal defect or patent ductus arteriosus, result in turbulent flow. The development of stenosis or insufficiency across a native valve is another important contributing factor. Prosthetic devices, such as biologic or mechanical valves and synthetic grafts, are a common site for infection. Chronic indwelling catheters and pacemaker leads traumatize the chambers and valves, damaging the endocardial surface.

### Development of Nonbacterial Thrombotic Endocarditis

The subendocardium becomes exposed to the circulation after the endocardium has been damaged. The subendocardium is thrombogenic, and platelets and thrombi become adherent in an attempt to heal the breach in the endocardium. This accumulation forms into a mass, or vegetation, that either remains adherent or embolizes to varying degrees.

### Transient Bloodstream Infection

The vegetation is a susceptible area for colonization by infectious organisms. Typically, there is a transient bacteremia resulting in bacterial deposition on the NBTE vegetation. Such transient bacteremia is common after oral cavity manipulation, upper or lower gastrointestinal (GI) endoscopy, urinary tract instrumentation, and childbirth. Percutaneous interventions and untreated skin infections are also sources of bacteremia. More invasive procedures produce a higher degree of bacteremia, and a longer duration and degree of bacteremia will allow more bacteria to adhere to the vegetation.

### Adherence of Organisms to Nonbacterial Thrombotic Endocarditis

The vegetation becomes infected when bacteria or other organisms adhere to the NBTE. The ability of various organisms to adhere to the NBTE is variable. Gram-positive bacteria such as *Staphylococcus* and *Streptococcus*, for example, have a greater ability to adhere and form endocarditis than gram-negative bacilli.

The platelets in the NBTE also have a role in bacterial adherence. Certain strains of bacteria that more commonly cause endocarditis have been shown to bind to and activate platelets.[5] This may occur through the release of thrombin-induced platelet-microbicidal proteins (tPMPs) by activated platelets. Bacteria can directly activate platelets or result in thrombin formation, which is a platelet agonist.[6]

### Growth of the Vegetation

After deposition and adherence to the NBTE, the bacteria grow and multiply, enlarging the vegetation. Recurrent or persistent bacteremia can reseed the vegetation, also contributing to progressive growth. Gross examination of the vegetation demonstrates a mass of bacteria, platelets, and fibrin (Fig. 38-1).

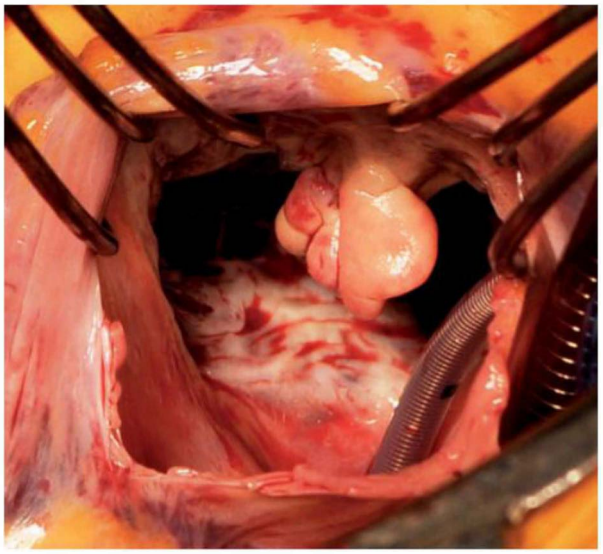


FIGURE 38-1 Vegetation on tricuspid valve exhibiting typical features of a mass of bacteria, fibrin, and platelets.

## EPIDEMIOLOGY

The overall incidence of IE in the general population ranges from 3 to 11 cases per 100,000 person-years.[7-9] About 75 percent of established cases occur in patients with an underlying structural defect of the heart.[10] Most commonly, these individuals have native valvular heart disease. Other common underlying conditions include previously implanted prosthetic valves and congenital heart disease. Endocarditis is more common in the elderly and males.[11]

Congenital heart disease represents a significant risk factor for the development of endocarditis. It has been estimated that the incidence of endocarditis in patients with any congenital heart defect is as high as 10 to 50 times the incidence of the general population. The most common congenital heart lesions associated with endocarditis are ventricular septal defect, transposition of the great arteries, tetralogy of Fallot, patent ductus arteriosus, and coarctation of the aorta. Those lesions with a cyanotic component are considered to be higher risk.

Mitral valve prolapse and bicuspid aortic valve are forms of congenital heart disease that most commonly present in older patients. The presence of a murmur is thought to be important to the development of endocarditis in these individuals, as the absence of a murmur is not associated with an increased prevalence in mitral valve prolapse.[12,13] Degenerative valve disease is also an important risk factor. The increasing use of indwelling intravenous catheters and leads for cardiac rhythm devices is associated with iatrogenic endocarditis.

## CLINICAL PRESENTATION

The clinical presentation of endocarditis depends upon the rapidity of onset, the virulence of the underlying organism, and the coexistence of underlying cardiac disease. More aggressive organisms in the setting of preexisting valvular disease will result in an accelerated course, with rapid diagnosis and early surgical intervention. Less virulent organisms may cause less destruction of cardiac structures, resulting in an elusive clinical course and prolonged illness.

### Acute Endocarditis

Patients with acute endocarditis usually present early in the infection with substantial illness. Findings include high fevers, chills, rigors, and malaise, with progression to sepsis and circulatory collapse if untreated. Complications are common (see following) due to the aggressive nature of the infection, particularly embolic phenomena. Valvular disease may be extensive with resultant congestive heart failure in otherwise healthy individuals.

### Subacute Endocarditis

The initial presentation in the subacute setting commonly occurs between 2 and 4 weeks after infection. The symptoms are milder and more subtle, with lower fevers and generalized malaise. Other symptoms include weight loss, myalgias, and fatigue, which can mimic malignancy or other chronic illness. If there has not been significant cardiac destruction, most symptoms will resolve on appropriate antibiotic therapy.

Many patients with subacute endocarditis will be diagnosed after a complication has arisen, such as an embolic neurologic event. Other complications of embolism include arterial insufficiency, abdominal pain (bowel or splenic infarction), visual changes (retinal artery occlusion), myocardial infarction (coronary artery occlusion), and hematuria (renal infarction). Multiple septic emboli to the lungs can present as recurrent pneumonia or chest pain from pulmonary infarction.

Two potentially lethal complications of subacute endocarditis are heart failure and intracranial hemorrhage. Although the infection may be successfully treated with antibiotics, the residual structural damage to the heart may progress to heart failure. Thus, a patient with "healed" endocarditis should not be considered cured unless the valvular and ventricular function is stable over a period of time. Mycotic aneurysms from septic emboli to the brain are usually asymptomatic, but can rupture and result in devastating intracranial hemorrhage.

### Prosthetic Valve Endocarditis

As with acute and subacute endocarditis, prosthetic valve endocarditis is classified according to time frame from

surgery. Early prosthetic valve endocarditis is defined as infection occurring within 60 days of operation, and is usually due to either intraoperative contamination or infection in the early postoperative period. Common organisms are skin colonizers and respiratory tract pathogens. The presentation is similar to acute endocarditis and is associated with complications after surgery. Late prosthetic valve endocarditis is defined as infection occurring after 60 days from operation and presents similar to subacute endocarditis. The offending organisms are the same as those with native subacute infections.

## Complications of Infective Endocarditis

The majority of patients with endocarditis will have developed complications, either as the initial presentation or during the course of the disease. The most common complications include congestive heart failure, abscess formation, and embolism. Other less common complications include pseudoaneurysm, mycotic aneurysm, fistula, and conduction disturbances.

Congestive heart failure is the most common cause of death and typically is caused by valvular destruction and insufficiency. Less common causes of congestive heart failure from endocarditis are coronary artery embolization with subsequent myocardial infarction, acute papillary muscle rupture, and valvular stenosis from very large vegetations. Patients with aortic valve disease are particularly prone to develop congestive heart failure.

Extension of the endocarditis process into surrounding myocardium results in abscess formation. This most commonly occurs with aortic valve involvement, forming a root abscess (Fig. 38-2). Mitral valve involvement can result in interventricular or interatrial abscess. Suspicion of abscess should be raised in patients with conduction abnormalities, pericarditis, congestive heart failure, and prosthetic valves. Transesophageal echocardiography (TEE) has the highest sensitivity for the detection of perivalvular abscess.[14] Echocardiographic criteria for abscess include aortic root thickness greater than 9 mm, perivalvular density greater than 14 mm in the septum, sinus of Valsalva aneurysm or fistula, and instability ("rocking") of a prosthetic valve.[15]

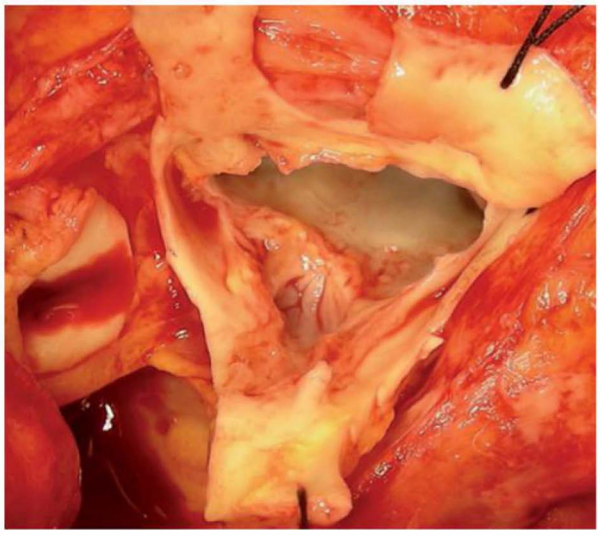


**FIGURE 38-2** Aortic root abscess. There is extension of the infection beyond the aortic annulus into the anterior leaflet of the mitral valve.

Embolism of the vegetation has the potential for significant morbidity and mortality, and is more common in younger patients.[16,17] Stroke occurs most commonly from native mitral valve endocarditis, as these lesions are usually larger than aortic valve vegetations.[18] In patients with prosthetic valve endocarditis, there is no difference in stroke rate between aortic and mitral valve involvement.[18] Predictors of stroke include left-sided endocarditis, mitral valve involvement, and size greater than 7 mm.[18]

Pseudoaneurysm occurs when the infective process liquefies and forms a cavity. Pulsatile pressure weakens the cavity and eventually blood enters the space, forming the pseudoaneurysm. The incidence of pseudoaneurysm ranges from 2 to 10 percent, and can occur in the setting of root abscess as well as along previous suture lines.[19] Rupture of pseudoaneurysm from IE is likely and requires prompt surgical attention.

Persistent bacteremia or embolization of infected vegetative material from the active endocarditis can result in metastatic abscess. Mycotic aneurysm occurs when a distant abscess forms in an arterial branch. Intracranial mycotic aneurysms typically form in the middle cerebral artery and can produce intracranial hemorrhage. Metastasis of infected material to other organs can result in splenic abscess, septic arthritis, and septic pulmonary embolism.

Fistula formation occurs when an abscess or pseudoaneurysm ruptures into a surrounding structure. Rupture into a cardiac chamber forms an intracardiac shunt, whereas rupture into the pericardium will produce tamponade. Although fistulas are rare, mortality exceeds 50 percent.[20]

Conduction abnormalities are the result of infective destruction of conduction tissue. First-degree atrioventricular block is most commonly observed.[21] Any new change in the electrocardiogram should raise the suspicion of abscess. Mortality can be increased in the presence of a conduction abnormality.[21]

## DIAGNOSIS

Although IE can be easy to recognize in a febrile patient with a new murmur, more commonly several physical and laboratory findings must be synthesized in order to establish an accurate diagnosis. In order to bring structure and validity to this process, Durack et al from Duke University proposed a set of diagnostic criteria in 1994. Modified by Li et al in 2000, these so-called "Duke criteria" are divided into *major* and *minor* categories.

Major criteria include positive blood cultures for IE, and evidence of endocardial involvement by echocardiography. Transesophageal echocardiography is recommended as a first test for patients with prosthetic valves, evidence of paravalvular abscess (e.g., new heart block), or a rating of at least "possible endocarditis" by clinical criteria. Transthoracic echocardiography is recommended in other patients. Minor diagnostic criteria include a predisposing condition (e.g., congenital heart disease or injection drug use), fever, evidence of embolic or immunologic phenomena, or equivocal microbiological findings.

The diagnosis of IE is established by the presence of two major criteria, one major and three minor criteria, or five minor criteria. Patients are diagnosed with "possible endocarditis" if they have one major and one minor criteria, or if they have three minor criteria. If a firm alternate diagnosis is established, or if a patient's symptoms resolve with less than 5 days of antibiotic therapy, the diagnosis of IE is rejected.

## History and Physical Examination

Adherence to the modified Duke criteria (Tables 38-1 and 38-2) during the initial evaluation provides the standard framework for establishing the diagnosis of endocarditis.[22–24] Important physical findings include cardiac murmurs, fever, signs of congestive heart failure, and peripheral manifestations. New or worsening murmurs signal valvular insufficiency. Fever is more common in patients with positive blood cultures.[25] Signs of congestive heart failure are important indicators of the severity of illness and possible need for early surgical intervention.

Peripheral manifestations of endocarditis include embolic, vascular and immunologic phenomena. Embolic arterial occlusion will result in diminished or absent pulses. Petechiae usually represent long-standing disease and are typically found in the conjunctivae, buccal mucosa, palate, and upper extremities. Osler nodes are small (0.5–1.5 mm), painful raised erythematous lesions found on the tips of the fingers and toes. In contrast, Janeway lesions are larger (2–5 mm), painless nodular erythematous lesions found on the palms of the hands and soles of the feet. Roth spots are oval-shaped hemorrhages on the retina with central pallor.

## Laboratory

There is no single laboratory test that is diagnostic for endocarditis. Multiple tests will support the diagnosis, including the presence of leukocytosis, anemia, elevated erythrocyte sedimentation rate, elevated c-reactive protein level, decreased serum complement levels, and presence of rheumatoid factor.

Blood cultures are the cornerstone laboratory test. In order to fulfill the Duke major criteria (Tables 1 and 2), the patient must have either a typical microorganism for IE isolated

**TABLE 38-1: Definition of Terms Used in the Proposed Modified Duke Criteria for the Diagnosis of Infective Endocarditis (IE)**

**Major criteria**
- Blood culture positive for IE
  - Typical microorganisms consistent with IE from two separate blood cultures:
    - Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*; or
    - Community-acquired enterococci, in the absence of a primary focus; or
  - Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
    - At least two positive cultures of blood samples drawn >12 h apart; or
    - All of three or a majority of >4 separate cultures of blood (with first and last sample drawn at least 1 h apart)
  - Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800
- Evidence of endocardial involvement
  - Echocardiogram positive for IE [TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE (paravalvular abscess); TTE as first test in other patients], is defined as follows:
  - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or abscess; or new partial dehiscence of prosthetic valve
  - New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

**Minor criteria**
- Predisposition, predisposing heart condition or injection drug use
- Fever, temperature >38°C
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
- Microbiological evidence: positive blood culture but does not meet a major criterion as noted above[a] or serological evidence of active infection with organism consistent with IE

TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

[a]Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

**TABLE 38-2: Definition of Infective Endocarditis (IE) According to the Modified Duke Criteria**

Definite IE
- Pathologic criteria
  1. Microorganisms demonstrated by culture or histologic examination of a vegetation that has embolized, or an intracardiac abscess specimen; or
  2. Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis
- Clinical criteria
  1. Two major criteria; or
  2. One major criterion and three minor criteria; or
  3. Five minor criteria

Possible IE
1. One major criterion and 1 minor criterion; or
2. Three minor criteria

Rejected
1. Firm alternate diagnosis explaining evidence of IE; or
2. Resolution of IE syndrome with antibiotic therapy for <4 days; or
3. No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for <4 days; or
4. Does not meet criteria for possible IE, as above

on two separate blood cultures or have persistently positive blood cultures drawn more than 12 h apart. In patients with unusual organisms, a single positive blood culture may be sufficient. More fastidious organisms or fungi may require several days or weeks to appear in the blood culture.

### Imaging

Plain chest radiography is nonspecific but important for associated findings of congestive heart failure. Cavitation or multiple infiltrates from septic pulmonary emboli may be identified. Computed tomography and magnetic resonance imaging (MRI) can be utilized to evaluate the complications of endocarditis, including stroke, mycotic aneurysm, and intra-abdominal processes. Cardiac MRI is particularly useful in complex valvular and abscess evaluation.

Echocardiography remains the diagnostic modality of choice for endocarditis. The hallmark is the vegetation, and echocardiography accurately defines the size, shape, and location of valvular vegetations. Intracardiac shunts, fistulae, and pseudoaneurysms can all be imaged with echocardiography.

TEE is superior to transthoracic echocardiography (TTE).[26] Specificity and sensitivity of TEE range from 88 to 100 percent and 86 to 100 percent, respectively.[27,28] The proximity of the TEE probe to the posterior wall of the heart provides better resolution, improved visualization of prosthetic valves, superior characterization of mitral valve disease, and finer assessment of abscess and fistula. Although TEE is more invasive and more expensive, it provides the optimal method for establishment of endocarditis according to the Duke major criteria.

In patients with a high likelihood of IE, TTE is usually sufficient to establish the diagnosis.[29] Similarly, TTE is technically adequate to establish a negative diagnosis in patients with a low likelihood of endocarditis.[29] Patients with an intermediate likelihood of endocarditis will have the most benefit from TEE, allowing for the definitive diagnosis.[29] TEE should be performed in every patient prior to operation unless contraindicated.

## MEDICAL THERAPY

Prompt and accurate antimicrobial therapy should be initiated for the patient with endocarditis. Ideally, this is instituted after the initial blood cultures have been obtained, and subsequent therapy is modified according to antibiotic sensitivities. The American Heart Association guidelines provide recommended antibiotic selections for various organisms and should be routinely consulted to guide therapy.[30,31] In general, antibiotic therapy will be administered intravenously in high dosages for a prolonged period of time. Drug resistance has become common and an experienced infectious disease consultation is advised.

Empiric antibiotics can be started and guided according to suspected organisms in specific patients. A combination of penicillin and gentamicin is reasonable, as this regimen will treat most of the common organisms. Suspicion of *Staphylococcus* will require substitution of a penicillinase-resistant agent such as nafcillin. Ampicillin may be added to cover the HACEK organisms. Intravenous drug users are susceptible to methicillin-resistant *Staphylococcus aureus*, and vancomycin and gentamicin are appropriate as initial therapy. Antifungal therapy should be considered in this population and any patient with critical illness that is not improving on standard antibiotic regimens, as these patients are at risk for fungal endocarditis.

## SURGICAL THERAPY

The primary goals of operation for endocarditis are removal of all infected tissue and correction of the hemodynamic abnormality. Inadequate drainage of infection results in a high probability of reinfection and subsequent complications. Infection of a cardiac valve necessitates either repair or replacement, and the surgeon must ensure that the surrounding tissue is healthy and viable in order to support any prosthetic material.

### Aortic Valve Disease

In general, endocarditis that affects the aortic valve will require valve replacement. It is the unusual patient that will have a small, localized perforation of a valve leaflet that

will be appropriate for patch reconstruction. Most patients will have destruction of the leaflets, which render the native valve unsuitable for repair, and replacement is indicated. There is no conclusive evidence to suggest that tissue bioprostheses have an advantage over mechanical prostheses for preventing reinfection.[31] Some recommend soaking the prosthetic valve in antibiotics or irrigating the area with antiseptic solutions.[32] After removal of the infected leaflets and debridement of the annulus, the new valve is inserted in standard fashion.

Careful inspection of the aortic root and anterior leaflet of the mitral valve should be performed simultaneously to evaluate for aortic root abscess or drop lesions on the mitral valve. All infected and necrotic tissue at the root must be removed. Stentless tissue valves, either xenografts or allografts, are more pliable than mechanical composite grafts and are useful to reconstruct continuity between the left ventricular outflow tract and the ascending aorta. It is important to be certain that the proximal suture line is well-seated in the left ventricular outflow tract, as this will exteriorize all infected tissue outside the blood stream.

Extension of the infection from the aortic root into the anterior leaflet of the mitral valve requires simultaneous reconstruction of the root and the mitral valve. This is accomplished with an allograft, keeping the attached anterior mitral leaflet intact. After removal of the root and construction of coronary buttons, the mitral valve is debrided. The retained allograft mitral leaflet is attached with running polypropylene suture to fill the defect in the mitral valve. The remainder of the allograft root is attached to the left ventricular outflow tract and the coronary buttons are reimplanted.

## Mitral Valve Disease

The mitral valve lends itself more often to reparative procedures. Perforations can be repaired with pericardial patch reconstruction (Fig. 38-3A). Destruction of the P2 segment of the posterior leaflet can be repaired with limited resection and sliding valvuloplasty, followed by posterior annuloplasty to support the repair (Fig. 38-3B). Drop lesions on the chordae tendineae can be carefully removed.

The presence of severe mitral insufficiency in the setting of endocarditis dictates valve replacement. Careful inspection is performed to evaluate for the presence of ventriculoatrial discontinuity. If there is annular abscess, all infected tissue must be removed. The annulus is reconstructed using a sheet of pericardium as a "bridge" between the ventricle and the atrium (Fig. 38-4A–C). The new valve is then secured to the ventricular aspect of this patch with pledgetted sutures.

## Tricuspid Valve Disease

The tricuspid valve can be repaired in nearly every patient with endocarditis. Patch closure of a perforation is performed in a similar manner to mitral valve perforations. More liberal leaflet excision can be accomplished on the tricuspid valve, and should be supported with complete annuloplasty.

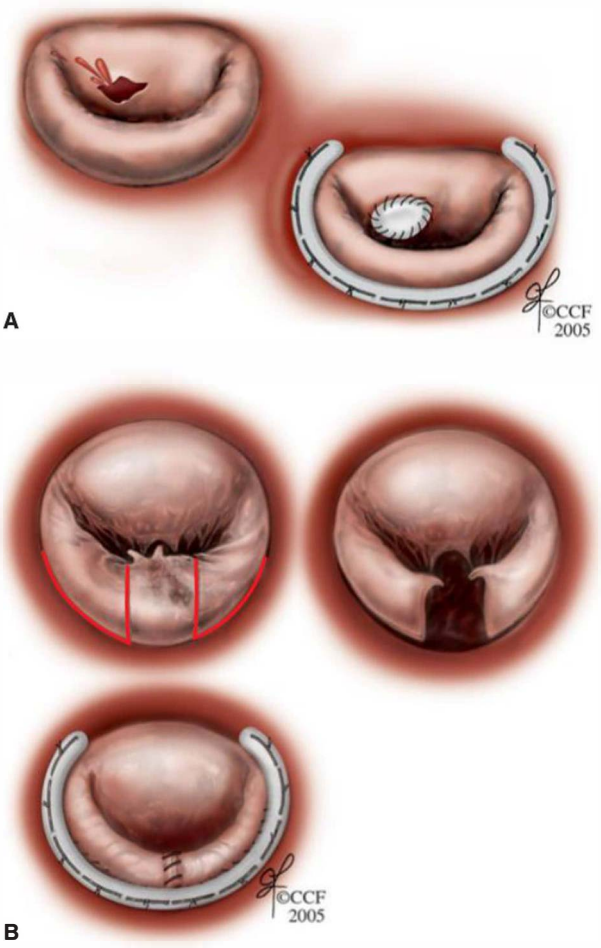



**FIGURE 38-3** **A.** Repair of mitral valve leaflet perforation with pericardial patch. (Reprinted with permission from © CCF 2005, Cleveland Clinic Foundation.) **B.** Posterior sliding mitral valve annuloplasty. (Reprinted with permission from © CCF 2005, Cleveland Clinic Foundation.)

## Sinus of Valsalva Fistula

Infection of the aortic valve with subsequent perforation of a sinus of Valsalva fistula can occur. After removal of all infected tissue, the fistula is explored. This may require opening of the secondary cardiac chamber for adequate visualization and debridement of additional infection. The fistula is closed with a pericardial patch and the aortic valve or root reconstructed as indicated.

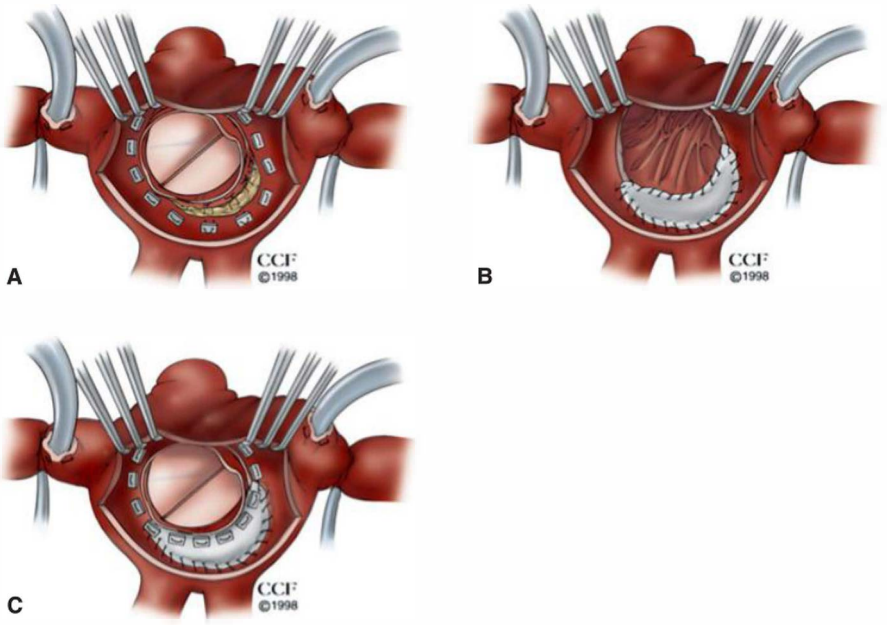



**FIGURE 38-4** **A.** Extensive destruction of posterior mitral annulus due to infection. **B.** Pericardial patch reconstruction of posterior mitral annulus. **C.** Implantation of prosthetic mitral valve using reconstructed posterior mitral annulus. (Reprinted with permission from CCF © 1998, Cleveland Clinic Foundation.)

## SURGICAL OUTCOMES

Mortality after operation for endocarditis ranges widely, with reports of hospital death between 4 and 30 percent.[33–36] In general, operative mortality is affected by the urgency of the operation, with emergency operations carrying the highest risk.[37] Concomitant preoperative heart failure and other comorbidities also have a negative impact on operative mortality.[37] Nonstreptococcal organisms and prosthetic valve endocarditis also are associated with increased mortality.[37] More complex operations, however, do not seem to adversely affect outcomes.[33,38] Late survival after operations for endocarditis are not as good as operations performed for other types of valvular disease.[39,40]

Heart block is more common after operation in patients with endocarditis than in those without infection. This is often predictable due to the extensive removal of infected tissue that may be required. A new or worsening neurologic deficit can be devastating and is most often due to aggravation of an existing central nervous system event. It is important to identify such preoperative findings and whether there is associated intracranial hemorrhage, as this worsens with anticoagulation during surgery. The risk of exacerbation of a neurologic deficit is highest if surgery is required within 1 week (44–46 percent), falls to 10 percent after 2 weeks, and declines further to 2 percent after 4 weeks.

Recurrent endocarditis is uncommon (2–5 percent) if all infected tissue has been removed and there is no active infection at the time of operation. Reinfection is more common if the organism is nonstreptococcal, there is a root abscess, or the patient is an intravenous drug abuser. For aortic native valve endocarditis, there is some evidence to suggest that replacement with an aortic allograft confers the best freedom from reinfection.[22,36] For all other types of native and prosthetic valve endocarditis, there is no evidence to suggest one type of prosthetic valve over another.

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## SURGICAL TREATMENT OF ENDOCARDITIS BOARD REVIEW QUESTIONS (CHAPTER 38)

1. Which of the following is *not* a major Duke criterion for the diagnosis of endocarditis?
   A. Two separate blood cultures positive for *Streptococcus bovis*
   B. Persistently positive blood cultures drawn 6 h apart
   C. Oscillating intracardiac mass on valve
   D. New valvular regurgitation
   E. Single positive blood culture for *Coxiella burnetii*

2. Which is correct regarding the pathogenesis of endocarditis?
   A. Damage occurs to the epicardial surface of a cardiac structure.
   B. There is accumulation of thrombus and platelets on the damaged surface.
   C. The patient develops a transient bloodstream infection.
   D. Infectious organisms deposit on the nonbacterial thrombotic focus.
   E. Organisms multiply at the infected site.

3. Which is correct regarding the clinical presentation of endocarditis?
   A. Acute endocarditis occurs up to 4 weeks after infection.
   B. Complications are more common in subacute endocarditis.
   C. Most symptoms resolve with appropriate antibiotic therapy in the subacute setting.
   D. Most mycotic aneurysms are symptomatic.
   E. Late prosthetic endocarditis is usually due to intraoperative contamination.

4. Which of the following is correct regarding complications of endocarditis?
   A. The minority of patients actually develop complications.
   B. The most common cause of congestive heart failure is coronary artery embolization.
   C. Embolism is more common in the elderly.
   D. Stroke is most common from a mitral valve vegetation.
   E. Rupture of a pseudoaneurysm is unlikely.

5. Which of the following is true for outcomes after surgery for endocarditis?
   A. Emergency operations do not have increased risk.
   B. Concomitant heart failure increases operative risk.
   C. Streptococcal organisms are associated with higher mortality.
   D. More complex operations result in higher complication rates.
   E. Mechanical valves are less likely to become reinfected.

## ANSWERS

1. **Answer: B.** Persistently positive blood cultures must be 12 hours apart to be considered a major criterion. Two separate blood cultures positive for *Streptococcus bovis*, an oscillating intracardiac mass on a valve, new valvular regurgitation, and a single positive blood culture for *Coxiella burnetii* are all considered major criteria.
2. **Answer: A.** Damage occurs to the endocardial, not epicardial, surface of a cardiac structure. After the damage occurs, there is accumulation of thrombus and platelets on the damaged surface (NBTE). The patient develops a transient bloodstream infection, usually bacterial, and these organisms deposit on the focus of the nonbacterial thrombotic area. Finally, organisms multiply at the infected site.
3. **Answer: C.** Most patients with subacute endocarditis will have resolution of symptoms with appropriate antibiotic therapy. Acute endocarditis is defined as occurring within 2 weeks of infection. Complications are more common in acute endocarditis. Most mycotic aneurysms are asymptomatic. Late prosthetic endocarditis is caused by the same organisms as native infections.
4. **Answer: D.** Stroke occurs mostly commonly from mitral valve vegetations, which tend to be larger and more mobile. The majority of patients develop complications from endocarditis. The most common cause of congestive heart failure is valvular insufficiency. Embolism is more common in the younger population. Rupture of a pseudoaneurysm from infection is likely and warrants prompt surgical intervention.
5. **Answer: B.** Concomitant heart failure is associated with increased operative risk, as are emergency operations and nonstreptococcal organisms. More complex operations do not adversely affect outcomes. There is no difference between mechanical and biologic prostheses for reinfection rates.

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# Ascending and Arch Aneurysms of the Aorta

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***"There is no disease more conducive to clinical humility than aneurysms of the aorta."***

—Sir William Osler

## KEY CONCEPTS

- Epidemiology
  - The leading cause of aneurysms of the ascending aorta is medial degeneration, which may be idiopathic or accelerated by heritable disorders of connective tissue; conversely, arch aneurysms are due to chronic dissection or long-standing hypertension and atherosclerosis.
- Pathophysiology
  - Histopathologic investigations of aneurysmal tissue have shown that a majority of ascending aortic and arch aneurysms are associated with medial degeneration in the layers of the aortic wall. This is characterized by a triad of (1) loss of noninflammatory smooth muscle cells, (2) fragmentation of elastic fibers, and (3) accumulation of basophilic ground substance in cell-depleted areas of the medial layer of the vessel wall. This combination of factors weakens the aortic wall, thereby increasing wall tension; this can induce aortic dilatation and aneurysm formation, leading to higher wall stress and eventually resulting in intramural hemorrhage, aortic dissection, or rupture. Medial degeneration can be accelerated by inborn errors of metabolism that affect any component of the aortic connective tissue. Known heritable disorders of connective tissue that commonly manifest as ascending and arch aneurysms of the aorta are Marfan syndrome, Ehlers–Danlos syndrome, Loeys–Dietz syndrome, familial forms of thoracic aortic aneurysm and dissection, and bicuspid aortic valve disease; Turner syndrome and Noonan syndrome occur far less frequently.
- Clinical features
  - Most patients with thoracic aortic aneurysms are asymptomatic at the time of presentation, and aneurysms of the ascending aorta usually are detected as incidental findings during testing for other disorders. In contrast, because of their anatomic location and the space-occupying nature of the aneurysm, aneurysms of the aortic arch may impinge on important mediastinal structures and are therefore symptomatic more often than aneurysms of the ascending or descending aorta. Symptoms attributable to the aneurysm are cause for concern and consideration for early surgical intervention. Patients with rupture of an ascending or arch aneurysm often present in extremis.
- Diagnostics
  - The most common finding on chest x-ray for a thoracic aortic aneurysm is widening of the superior mediastinum; other findings include displacement and compression of the mediastinal contents and curvilinear calcification in the aneurysmal wall. Echocardiography is widely available, can be noninvasive [transthoracic echocardiography (TTE)] or minimally invasive [transesophageal echocardiography (TEE)], and is relatively inexpensive. TTE can visualize the aortic root and ascending aorta accurately and is suitable for evaluating the size of moderate aneurysms and assessing cardiac complications such as aortic regurgitation (AR), impaired left ventricular function, and hemopericardium. Intraoperative application of TEE allows continuous monitoring of the surgical procedure without disturbing the sterile field. Because of its speed and wide availability, computed tomography/computed tomography angiography (CT/CTA) is currently the most common diagnostic

imaging method for studying the aorta. CTA has the advantage of demonstrating aortic wall thickening, calcification, and luminal thrombus, thus displaying the true axial extent of an aneurysm. Magnetic resonance angiography is emerging as a diagnostic tool but is less readily available and has limited utilization in acute aortic problems because of its limited applicability.

- Treatment
  - Symptomatic patients with ascending or arch aneurysms should be evaluated urgently for surgical repair. Patients presenting with rupture should be operated on urgently, since these conditions are almost uniformly fatal without prompt surgical intervention. Operative intervention in a patient with a non-heritable connective tissue disorder should be considered when the ascending aortic aneurysm diameter ranges from 5 to 5.5 cm. For patients with an aneurysm diameter less than 5 cm who are being monitored with serial imaging, an indication for surgical intervention would be a 10 percent increase in size over a 6- to 12-month time course. For patients with a heritable disorder of connective tissue, surgical intervention for the ascending aorta should be considered at a diameter of 4 cm for Loeys–Dietz syndrome, 4 to 4.5 cm for Marfan syndrome, 4.5 to 5.0 cm for bicuspid aortic valve, and 5.0 cm for Ehlers–Danlos syndrome. Factors that prompt the recommendation for surgery when the aorta is less than 5.0 cm include rapid growth of the aortic diameter (more than 1 cm/year), a family history of premature aortic dissection (dissection at less than 5.0 cm), and the presence of moderate or severe AR. Operative repair varies with the underlying pathology and the quality of the aortic wall, the status of the aortic valve, expected survival, and the general well-being of the patient.
- Outcomes
  - Progress over the past three decades, including improved surgical instrumentation and advances in perfusion strategies with resultant improvements in myocardial and cerebral protection have augmented the surgical armamentarium significantly, facilitating the management of complex aortic problems. Replacement of the ascending aorta is a safe and effective procedure, with operative mortality rates of 2 to 5 percent. The operative mortality varies with the acuity of the operation, patient age, left ventricular function, and extent of operation. Late survival after operation is approximately 65 percent at 5 years and 55 percent at 7 years. For patients with Marfan syndrome, a valve-sparing aortic root replacement is a reasonable alternative to a composite valve graft. Survival is excellent with reimplantation and remodeling techniques and complications are rare, but the long-term durability of these repairs have not been established. For aortic arch replacement, the average operative mortality rate is 13 percent, with long-term survival ranging from 61 to 82 percent at 5 years and 31 to 69 percent at 10 years. Despite these advances, providing adequate cerebral protection and preventing cerebral embolization during reconstruction of the calcified and atherosclerotic aorta are formidable challenges.

# INTRODUCTION

Surgical repair of ascending and arch aneurysms of the aorta is one of the most formidable challenges facing the cardiovascular surgeon. The challenges stem from the often-catastrophic consequences of rupture of the thoracic aorta, the variegated clinical presentations associated with aortic disruption, and the risk of incurring devastating neurologic injury during aortic arch repair. This chapter describes the epidemiology, pathophysiology, clinical features, diagnosis, treatment, and outcomes of ascending and arch aneurysms of the aorta.

## Definitions

A *true* aortic aneurysm is defined arbitrarily as a 50 percent enlargement of the normal aorta for a particular body surface area, age, and gender.[1] Clinically, the term usually is reserved for ascending aortic (sinus or tubular) diameters greater than 3.5 to 4.0 cm or aortic arch diameters greater than 4 cm. Some experienced thoracic aortic surgical centers use a ratio of 2× in which the diameter of the enlarged aortic segment is in the numerator and that of the normal contiguous aorta is in the denominator.[2] The combination of dilation of the ascending aorta and dilation of the aortic annulus is termed *annuloaortic ectasia*.[3] A *false* aortic aneurysm is a localized dilation whose wall consists of adventitia, some or all of the media, and compressed periaortic tissue usually associated with trauma, infection, or previous operations on the aorta. The classification of thoracic aortic aneurysms is based on the location, morphologic characteristics, or etiology.[4]

### CLASSIFICATION ACCORDING TO LOCATION

The location of the aneurysm affects clinical manifestations, natural history, and treatment options as well as providing insight into the etiology of the aneurysm formation. Thoracic aortic aneurysms can involve the ascending aorta, the arch, or the descending aorta. The ascending aorta is the portion of aorta starting at the aortic annulus and ending at the origin of the innominate artery near the pericardial reflection. The ascending aorta is separated further into a

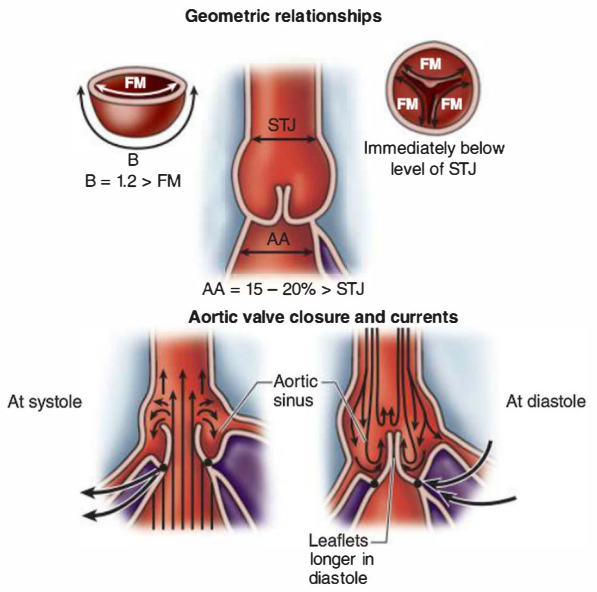



**FIGURE 39-1** The static and basic functional anatomy of the aortic root-valve complex. Note that the sinotubular junction diameter is approximately 15 percent less than that of the base of the aorta (putative aortic annulus). The DaVinci sinus currents are depicted; they enhance leaflet closure at the end of systole and protect leaflets from wall impact during systole. In addition, movement of the annulus changes the tension–length relationships of the leaflets to enhance function. It is difficult to demonstrate in a two-dimensional figure the time-dependent expansion of the aortic root that occurs during the first third of systole and the change in its overall configuration from a truncated cone shape with acorn protuberances of the sinuses to a larger, more cylindric form that would offer less impedance to ejection. FM, free margin; B, base of semilunar leaflet insertion; STJ, sinotubular junction; AA, aortic annulus (defined as the base of the aorta, not the semilunar leaflet attachment scalloped edge). (Reproduced, with permission, from Hopkins RA. Aortic valve leaflet sparing and salvage surgery: Evolution of techniques for aortic root reconstruction. *Eur J Cardiothorac Surg* 2003;24(6):886–897.)

proximal sinus portion, also known as the aortic root, and a distal tubular portion, with the demarcation line occurring at the sinotubular junction (STJ), which is at the top of the aortic valve commissures (Fig. 39-1). These distinctions are important in that operations involving the aortic root require repair or replacement of the aortic valve and reimplantation of the coronary arteries. The aortic arch begins at the proximal origin of the innominate artery, traverses in conjunction with the brachiocephalic vessels, and ends at the distal origin of the left subclavian artery, dividing the aortic arch into the proximal, transverse, and distal sections, respectively. Aneurysms of the descending thoracic aorta originate distal to the origin of the left subclavian artery, whereas thoracoabdominal aneurysms originate in the descending thoracic aorta and extend below the diaphragm to involve various extents of the abdominal aorta.

### CLASSIFICATION ACCORDING TO MORPHOLOGY

The gross pathoanatomic description of thoracic aortic aneurysms includes fusiform and saccular aneurysms. Fusiform aneurysms involve a long segment of the aorta with uniform dilation involving the whole circumference of the aortic wall, whereas saccular aneurysms usually involve only a localized segment of the aorta with an eccentric dilation that communicates with the main lumen of the aorta by a variable-sized neck.[4]

### CLASSIFICATION ACCORDING TO ETIOLOGY

Classification by etiology provides the most meaningful nomenclature for thoracic aortic aneurysms because of the treatment implications but at the same time is the most difficult to do. This stems from the variety of causes of thoracic aortic aneurysms, which histologically look very similar. The leading cause of aneurysms of the ascending aorta is medial degeneration, which may be idiopathic or accelerated by heritable disorders of connective tissue; conversely, arch aneurysms are due to chronic dissection or long-standing hypertension and atherosclerosis. This is discussed in more detail in the pathophysiology section.

## Historical Highlights

The first description of arterial aneurysms is attributed to Galen, who observed false aneurysms in gladiators injured during battle in the second century. During that period, Antyllus made the distinction between traumatic and degenerative aneurysms and was the first to attempt surgical treatment of aneurysms with proximal and distal ligation.[5] In 1557, Vesalius[6] was credited with the first correct clinical diagnosis, and Morgagni outlined fascinating and detailed case histories, postmortem findings, and commentaries on three cases of ruptured thoracic aneurysms in young adults in 1769. In his great work *The Seats [Sites] and Causes of Diseases*, he described the graphic case report of a "strumpet [prostitute] of eight-and-twenty years of age" who died suddenly in the act of performing her profession, causing considerable embarrassment to her client.[7]

The early operative treatment of thoracic aneurysms was entirely palliative, consisting of the introduction of wire within the sac to stimulate clot formation or the wrapping of cellophane around the sac to induce periarterial fibrosis. Before the availability of cardiopulmonary bypass (CPB), surgical treatment of thoracic aortic aneurysms was limited to resection of discrete saccular aneurysms associated with coarctations.[7] Even though the first isolated thoracic aneurysm of the arch was resected by Monod and Meyer in Paris in 1950,[8] the development of current aortic surgery procedures was contingent on improvements in vascular surgical instruments and the evolution of arterial grafts and bypass procedures in conjunction with CPB and the various perfusion techniques.

### ASCENDING ANEURYSMS

Cooley and DeBakey[9] are credited with the first resection of an ascending aortic aneurysm and replacement with a graft in 1956; subsequently, a variety of approaches evolved. In 1960, Mueller and colleagues[10] combined supracoronary graft replacement with bicuspidization of an incompetent aortic valve. In 1963, Starr and associates[11] described supracoronary graft replacement and replacement of the aortic valve. In 1964, Wheat and coworkers[12] described a technique of radical resection of the aortic wall that left small buttons of tissue adjacent to the coronary ostia, replacement of the aorta with a graft, and prosthetic replacement of the aortic valve. Bentall and DeBono[13] and, independently, Edwards and Kerr[14] introduced a method of replacing the aortic valve and ascending aorta simultaneously using a composite valve graft (CVG) and reimplanting the coronary ostia into the graft. After 1968, the CVG procedure evolved to include full-thickness end-to-side coronary anastomoses in the form of Carrel "buttons" of aorta and a full-thickness end-to-end distal aortic anastomosis rather than the original "wrap inclusion" or Bentall technique.[2]

### ARCH ANEURYSMS

Resection of aortic arch aneurysms has remained a more formidable surgical challenge. In 1957, DeBakey and colleagues[15] reported the first successful replacement of an ascending and arch aneurysm with an aortic homograft, using CPB with separate innominate and left common carotid artery perfusion. Bloodwell and associates[16] modified the basic CPB technique in 1968 to perfuse the carotid and vertebral arteries separately and implant the arch vessels together as a single "button." Griepp and associates[17] at Stanford first used the technique of circulatory arrest for complete replacement of the aortic arch in 1975 with implementation of the "open distal." In 1983, the "elephant trunk" technique was introduced by Borst and associates[18] as an alternative for the treatment of patients with extensive aortic aneurysmal disease involving the arch and the descending or thoracoabdominal aorta.

## Basic Embryology and/or Anatomic Considerations

At one stage of development, two aortic arches (right and left) are present with normal development, including persistence of the left arch and involution of the right arch. Originating from the aortic arch are branching vessels, with many variations in both the number and the position of those vessels. Permutations may be as few as one or as many as six branches, with these anomalies intimately associated with the development of the fourth arterial arches (Fig. 39-2A). In about 80 percent of people, the branching order is innominate, left common carotid, and left subclavian; however, in 11 percent of these patients, a bovine arch exists where the innominate and the left common carotid have a common ostia and the left subclavian arises independently from the arch (Fig. 39-2B).[19,20] Aberrant right subclavian artery (ARSCA) affects approximately 0.1 percent of the population and is often an incidental finding on imaging studies. It occurs when the right fourth aortic arch and the right dorsal aorta involute cranial to the seventh intersegmental artery.[21] The ARSCA arises from the descending aorta or a diverticulum and crosses to the right behind the esophagus (Fig. 39-2C). Surgeons must be aware of the possible variations in the great vessels arising from the aortic arch because misidentification during surgery could be catastrophic.

# PATHOPHYSIOLOGY

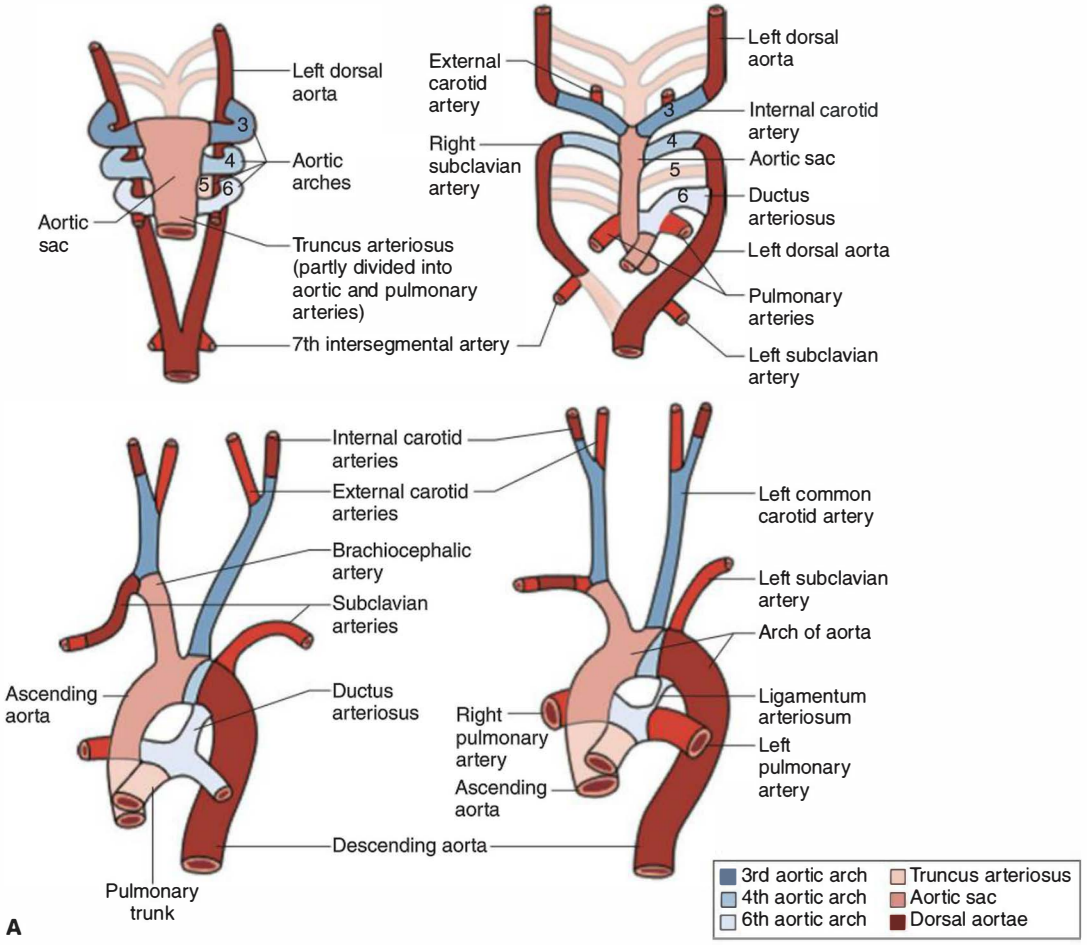
## Introduction

The aortic wall is organized into three distinct layers: the intima, media, and adventitia (Fig. 39-3). The media of the aorta is composed of smooth muscle cells within a matrix of elastin, collagen, and other structural proteins, including fibrillin, laminin, glycosaminoglycans, proteoglycans, and fibronectin. The overall strength of the aortic wall is determined by the relative amounts of elastin and collagen; elastin conveys the arterial recoil capabilities, and collagen provides the necessary structural strength. Defects in either protein can cause aortic pathology.[22] Table 39-1 lists the etiologies of thoracic aortic aneurysms; these entities and their clinical implications are described in the following section.

## Medial Degeneration

### IDIOPATHIC MEDIAL DEGENERATION

Histopathologic investigations of aneurysmal tissue have shown that the majority of ascending aortic and arch aneurysms are associated with medial degeneration in the layers of the aortic wall.[23,24] These degenerative changes within the aortic media, which historically and incorrectly were called medial necrosis or cystic medial necrosis,[25] are characterized by a triad of (1) loss of non-inflammatory smooth muscle cells, (2) fragmentation of elastic fibers, and (3) accumulation of basophilic ground substance in cell-depleted areas of the medial layer of the vessel wall. This combination of factors first weakens the aortic wall, thereby increasing the wall tension, which can induce aortic dilatation and aneurysm formation. In turn, this leads to higher wall stress, eventually resulting in intramural hemorrhage, aortic dissection, or rupture. Medial degeneration occurs normally to some extent with aging, but the process is accelerated by hypertension.[26] In addition, turbulent flow within the aneurysm cavity frequently leads to the formation of laminated thrombus and further atherosclerotic depositions in the aortic wall. The thrombus lining and aortic calcifications, although often substantial, convey no added strength for the prevention of rupture.[22]



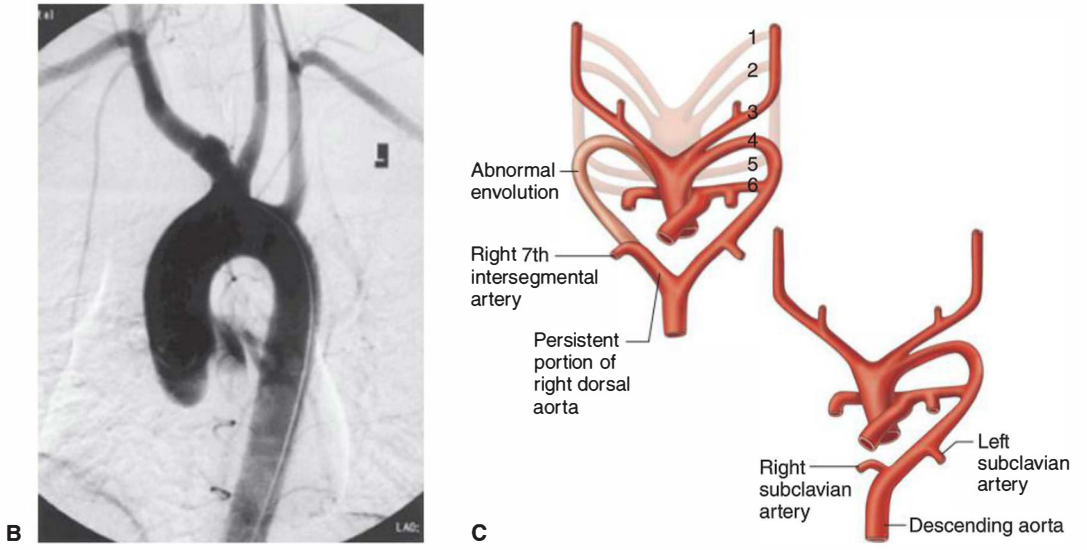




**FIGURE 39-2** Arch development and anomalies. **A.** Diagrams showing transformation of the early aortic arch pattern (6–8 weeks) into the adult pattern. (Reproduced with permission from Moore KL. *The Developing Human: Clinically Oriented Embryology*. Philadelphia: WB Saunders Co., 1982.) **B.** Aortogram demonstrating a bovine arch with a pseudoaneurysm near the origin of the innominate artery. (Reproduced with permission from Jweied E, Fogelson B, Fishman D, Merlotti G. Blunt injury of the innominate artery associated with a bovine arch. *J Trauma* 2002;52(5):1002–1004.) **C.** Diagram showing the embryologic basis of an aberrant right subclavian artery. (Reproduced with permission from Moore KL. *The Developing Human: Clinically Oriented Embryology*. Philadelphia: WB Saunders Co., 1982.)

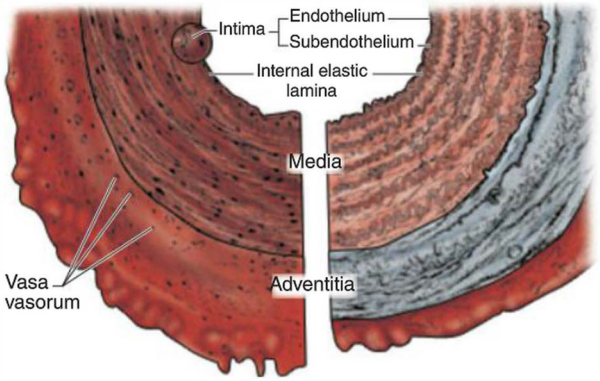



**FIGURE 39-3** Artery wall. Diagrams of a muscular artery prepared by hematoxylin and eosin (H&E) staining (*left*) and an elastic artery stained by Weigert's method (*right*). The tunica media of a muscular artery contains predominantly smooth muscle, whereas the tunica media of an elastic artery is formed by layers of smooth muscle intercalated by elastic laminae. The adventitia and the outer part of the media have small blood vessels (vasa vasorum) and elastic and collagenous fibers. (Reproduced with permission from Junquiera LC. *Basic Histology Text and Atlas*, 11th ed. New York: McGraw-Hill, 2005.)

## HERITABLE DISORDERS OF CONNECTIVE TISSUE

Medial degeneration is accelerated by inborn errors of metabolism that affect any component of the aortic connective tissue (i.e., ground substance, collagen, elastin, or smooth muscle cells). Known heritable disorders of connective tissue that commonly manifest as ascending and arch aneurysms of the aorta are Marfan syndrome (MFS), Ehlers–Danlos syndrome (EDS), Loeys–Dietz syndrome (LDS), familial forms of thoracic aortic aneurysm and dissection, and bicuspid aortic valve (BAV) disease; Turner syndrome and Noonan syndrome occur far less frequently.

**TABLE 39-1: Etiology of Ascending and Arch Aortic Aneurysms**

Medial degeneration
- Idiopathic degeneration
- Heritable disorders of connective tissue
  - Marfan syndrome (MFS)
  - Ehlers–Danlos syndrome (EDS)
  - Loeys–Dietz syndrome
  - Familial thoracic aortic aneurysms and dissections (TAAD)
  - Bicuspid aortic valve (BAV)
  - Turner and Noonan syndromes

Infection
- Mycotic aneurysms
- Syphilitic aneurysms

Inflammatory
- Takayasu arteritis
- Behçet disease
- Giant cell arteritis

Chronic aortic dissection

***Marfan Syndrome.*** Among hereditary diseases, MFS is the most prevalent inherited connective tissue disorder, with a prevalence of approximately 1 in 3000 to 5000 individuals. The diagnosis is clinical, relying on the revised Ghent consensus criteria.[27] The condition is inherited in an autosomal dominant manner with complete penetrance but demonstrates variable expression with significant intra- and interfamilial variation (Fig. 39-4).[2] More than 100 mutations have been identified in the fibrillin-1 gene on chromosome 15, as well as more recently identified missense mutations in the transforming growth factor β (TGF-β) gene, which encodes for the TGF-receptor. As a result, defective coding of fibrillin, the major structural component of elastin, occurs as well as excessive TGF-β activity. The consequence is both a decrease in the amount of elastin in the aortic wall and a loss of the normally highly organized structure of elastin (Fig. 39-5). In addition, Marfan aortic tissue has enhanced expression of metalloproteinases, which may promote both fragmentation of medial elastic layers and elastolysis.[28] The end result is an aorta that exhibits markedly abnormal elastic properties that lead to progressive increases in stiffness and dilation. Additional cardiovascular complications include mitral valve prolapse and regurgitation and left ventricular dilation, but aortic root dilation is the most common cause of morbidity and mortality.

***Ehlers–Danlos Syndrome.*** EDS is a rare autosomal dominant inherited disorder of connective tissue that results from mutations in the *COL3A1* gene, which encodes for type III collagen on chromosome 2. The classification of EDS has been simplified into six major types, including vascular EDS (formerly known as type IV EDS), which carries a substantial risk of rupture of the aorta and its major branches.[29] Arteries in the thorax and abdomen account for 50 percent of the vascular complications,[30] but any anatomic location can be involved, with a predilection for medium-size arteries.

***Loeys–Dietz Syndrome.*** The LDS is a recently described autosomal dominant aortic aneurysm syndrome that has widespread systemic involvement.[31] A spectrum of mutations in transforming growth factor β receptors 1 and 2 (*TGFBR1* or *TGFBR2*, respectively) cause the LDS, which histologically results in a loss of elastin content and disarrayed elastic fibers in the aortic media.[32] The phenotype of LDS overlaps with that of MFS (aortic aneurysm, arachnodactyly, dural ectasia), but it also includes distinctive features such as widely spaced eyes (hypertelorism), bifid uvula and/or cleft palate, and generalized arterial tortuosity. The natural history of LDS differs considerably from other connective tissue disorders with the average age at a first cardiovascular event much lower than that for patients with untreated MFS or vascular EDS, suggesting that mutations

| Criterion | Major | Minor |
|---|---|---|
| **Skeleton system** | | |
| Manifestations | Pectus carinatum or pectus excavatum surgery, arm span to height ratio >1.05 or reduced US/LS* <0.86 (adults), positive wrist and thumb sign, scoliosis >20° or spondylolthesis, limited elbow extension (<170°), pes plaxus | Facial appearance, joint hypermobility, pectus excavatum of moderate severity, highly arched palate |
| Involvement | 4 of 7 present | 2 of 7 major present, or 1 of 7 major and 2 of 4 minor present |
| **Ocular system** | | |
| Manifestations | Ectopia lentis | Myopia, flat cornea, iris or ciliary muscle hypoplasia |
| Involvement | Ectopia lentis present | 2 of 3 minor present |
| **Cardiovascular system** | | |
| Manifestations | Dilation of ascending aorta with or without aortic regurgitation and involving sinuses of Valsalva, dissection of ascending aorta | Mitral valve prolapse, annulus mitralis calcification (age of onset, <40 y), pulmonary artery dilation, dilatation or dissection of descending thoratic or abdominal aorta (age of onset, <50 y) |
| Involvement | 1 of 2 present | 1 of 4 minor present |
| **Pulmonary system** | | |
| Manifestations | | Pneumothorax, apical blebs (chest radiography) |
| Involvement | | 1 of 2 minor present |
| **Skin** | | |
| Manifestations | | Striae atrophicae (not associated with weight changes or pregnancy), recurrent or incisional hernias |
| Involvement | | 1 of 2 minor present |
| **Dura** | | |
| Manifestations | Lumbossoral dural ectasia bt CT or MRI | |
| Involvement | Dural ectasia present | |
| **Family** | | |
| Involvement | First-degree familiy member independently fulfilling diagnostic criteria, mutation in *FBNI* known to cause MPS | |

*US/LS indicates ratio of upper segment to lowe segment.

**FIGURE 39-4** Diagnostic criteria according to the Ghent nosology (From Milewicz DM, Dietz HC, Miller DC. Treatment of aortic disease in patients with Marfan syndrome. *Circulation* 2005 22;111(11):e150–e157. With Permission).

in *TGFBR1* or *TGFBR2* predispose to more aggressive and widespread vascular disease.

***Familial Thoracic Aortic Aneurysms and Dissections.*** It is coming to be known that patients without genetic syndromes such as MFS or EDS also manifest familial clustering of thoracic aortic aneurysms and dissections (TAAD). In the Yale database of over 1600 patients, detailed family trees of 300 families revealed that 21 percent of aneurysm probands have a first-order relative with a known or likely aortic aneurysm.[33] Most pedigrees suggest an autosomal dominant mode of inheritance, but there is marked variability in the expression and penetrance of the disorder in which some inherit and pass on the gene but show no manifestation of the disease. These nonsyndromic patients have been studied, and to date three genomic loci for nonsyndromic familial TAAD have been elucidated: the TAAD1 locus mapped to the long arm of chromosome 5, with approximately half of the identified families mapping to this locus; the FAA1 locus on the long arm of chromosome 11, which is responsible for aneurysmal disease in one large family; and the MFS2 locus on chromosome 3, which is a rare cause of familial TAAD.[4] Therefore, TAAD is now a recognized heritable disorder of connective tissue.

***Turner and Noonan Syndromes.*** Turner syndrome is a sex aneuploidy syndrome in which the most common chromosome constitution is 45-X0; it has an incidence of 1 in 5000 live female births. The cardiovascular problems include BAV (present in one-third of subjects), coarctation of the aorta,

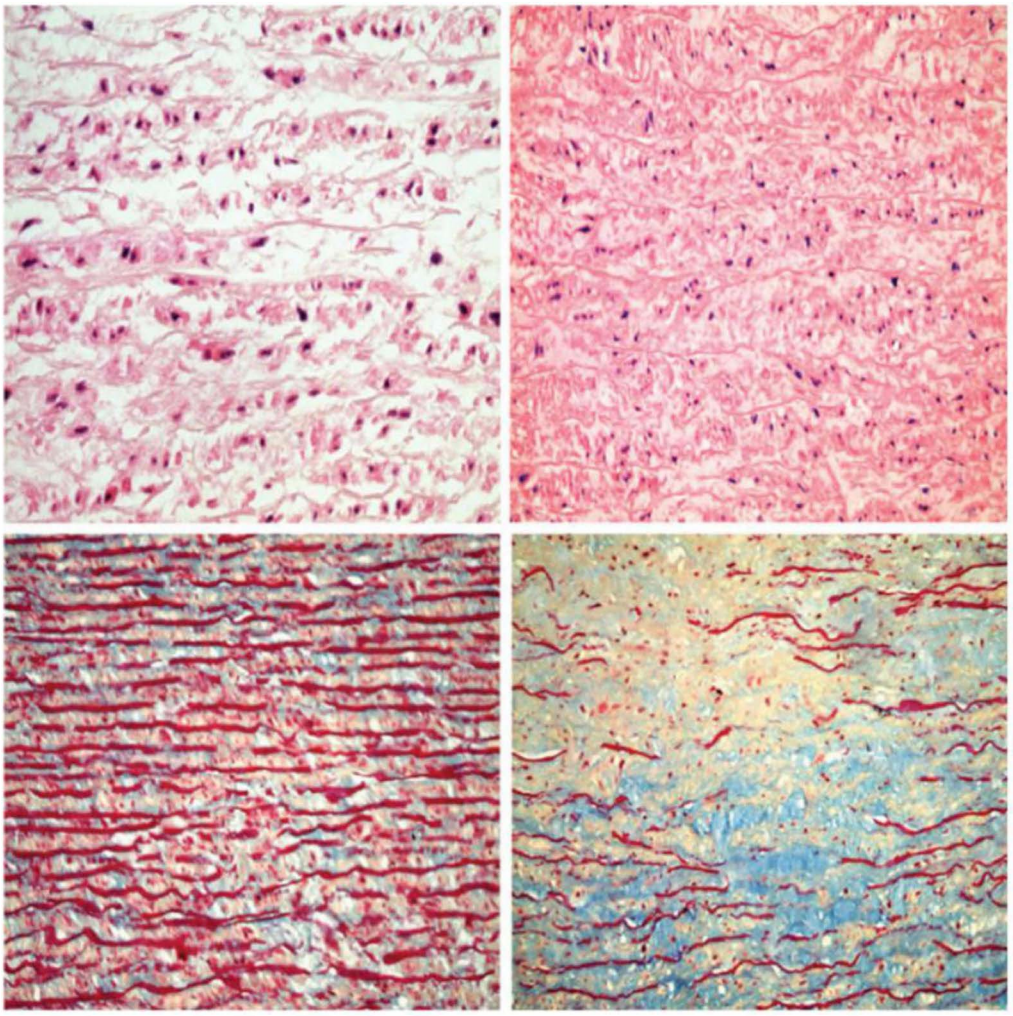


**FIGURE 39-5** Histology. Normal aorta stained with hematoxylin and eosin (H&E) × 120 (*upper left*) showing uniform distribution of elastin layers and fibromyocytes between them and Alcian blue/fuchsin/picric acid stain × 120 (*lower left*) with elastin stained red, fibromyocytes pale khaki-colored, and connective tissue pale gray–blue. Erdheim disease of the aorta stained with H&E × 120 (*upper right*) shows irregular distribution of fibromyocytes with irregularity and loss of elastic lamellae. In the lower right, Alcian blue/fuchsin/picric acid stain × 120 shows disruption and loss of elastic lamellae (*red*) and a hyperabundance of acidic mucin (*green–blue*).

hypertension, and TAAD. Aortic root dilation is present in approximately 40 percent of Turner syndrome patients. Another rare genetic disorder that occasionally predisposes to aortic aneurysms is Noonan syndrome, an autosomal dominant condition.

***Bicuspid Aortic Valve Disease.*** BAV is the most common congenital heart malformation, with a population prevalence of 1 to 2 percent. It is not clear whether BAVs are heritable, but groups have shown that there is a high incidence of familial clustering that is compatible with an autosomal dominant inheritance pattern with reduced penetrance.[34–36] Familial aggregation studies have indicated that 9.1 percent of persons with BAV have a first-degree relative with BAV, with males and females equally affected.[36] The clinical consequences of BAV disease focus on either valvular (stenosis, insufficiency, or infection) or vascular (dilation or dissection) complications. Sabet and coworkers[37] performed a large pathologic review and revealed that BAV disease results in a stenotic lesion in three-quarters of patients, insufficiency in 15 percent, and a mixed lesion in 10 percent. The vascular complications of BAV disease are less well understood, but the presence of BAV is an independent risk factor for progressive aortic dilation, aneurysm formation, and dissection.[38] In fact, BAV disease carries a 9- to 18-fold higher incidence of ascending aortic dilation.[39,40] The cause of this association initially was attributed to "poststenotic dilation," with high-velocity turbulent flow distal to a stenosis leading to downstream dila-

tion. However, advances in molecular biology have offered new insights that implicate intrinsic abnormalities of the aortic wall as being responsible for the pathologic development of aortic dilation. Embryologically, the aortic valvular cusps and ascending arterial media both arise from common neural crest cells during development. Apoptosis of those neural crest derivatives, specifically premature vascular smooth muscle cell apoptosis within the aortic media, is present in ascending aortic aneurysms of BAV carriers.[41,42] In addition, fibrillin-1 deficiency in the aortic media of BAV patients has been implicated in triggering matrix metalloproteinase (MMP) production, leading to matrix disruption and thus aortic dilation (Fig. 39-6).[43] The cause of BAV is unknown, but it is associated with accelerated degeneration of the aortic media, indicating that BAV disease is an ongoing pathologic process, not a discrete developmental defect.[44]

## Chronic Aortic Dissection

Both Stanford type A and type B chronic aortic dissections tend to dilate over time. The natural history starts with a vulnerable aortic wall at baseline, which is stressed with the tearing of the intimal flap, leaving the structural integrity of the aorta destabilized to only the weakened outer wall of the false lumen. Consequently, those with chronic aortic dissection are at high risk for aneurysm formation. Debakey and colleagues found that aneurysms developed in 46 percent of patients with uncontrolled hypertension but in only 17 percent with controlled hypertension.[45] Recently, Griepp and coworkers found that after repair of acute type A dissections, the growth of the distal aorta averaged 0.85 mm a year for the aortic arch and 1.24 mm a year for the descending thoracic aorta.[46]

## Infection

### MYCOTIC ANEURYSMS

Osler[47] adopted the term *mycotic* to denote aneurysms originating on the basis of infection.[48] Mycotic aneurysms of the thoracic aorta are rare but can be fatal if they are not diagnosed early. Bacterial seeding of the aortic wall can occur by hematogenous spread to the intima or the vasa vasorum, lymphatic spread, or direct extension from an adjacent infected focus. The thin endothelial intimal lining of the aorta is generally highly resistant to infection, but disruption of this barrier by atherosclerosis reduces resistance to infection.[49] Epidemiologically, this disease, which traditionally has been due to endocarditis, now has an increased tendency to afflict the elderly, possibly as a result of an atherosclerotic load facilitating infection. Aneurysms are usually saccular and well localized, with *Staphylococcus aureus* and *Salmonella* species being the predominant organisms. Surgery with complete excision and debridement of infected tissue with in-line aortic reconstruction is the definitive treatment. Lifelong prophylactic antibiotic therapy may be advisable to prevent recurrences unless there is a clearly identifiable and treatable source of infection.

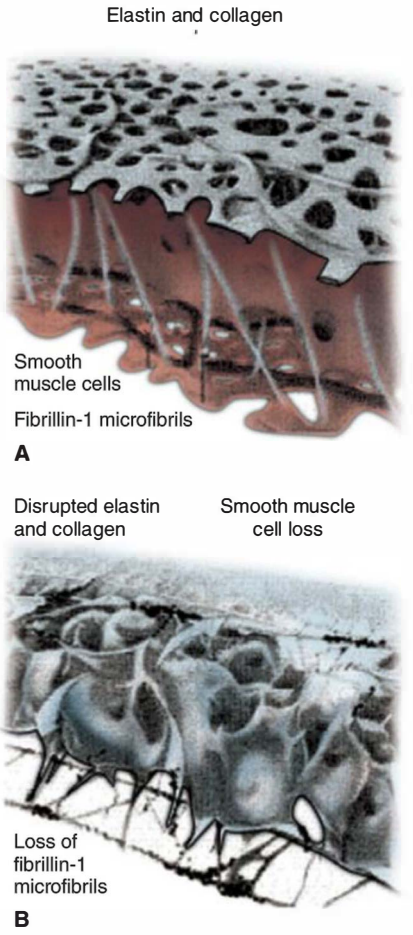



**FIGURE 39-6** The elastic laminae of the aortic media provide structural support and elasticity to the aorta. In normal tricuspid valve patients (**A**), fibrillin-1 microfibrils tether smooth muscle cells to adjacent elastin and collagen matrix components. In patients with BAV (**B**), deficient microfibrillar elements result in smooth muscle cell detachment, matrix metalloproteinase release, matrix disruption, cell death, and a loss of structural support and elasticity. (Reproduced, with permission, from Fedak PW, Verma S, David TE, et al. Clinical and pathophysiological implications of a bicuspid aortic valve. *Circulation* 2002;106(8):900–904.)

### SYPHILITIC ANEURYSMS

Syphilis was once perhaps the most common cause of ascending aortic aneurysms, but in an era of aggressive antibiotic treatment, such luetic aneurysms are seen rarely in medical centers.[50] Syphilitic aortitis is a chronic mesarteritis and periarteritis of the aorta, with patchy destruction and scarring of musculoelastic medial tissue and replacement by vascularized connective tissue.[48] The complications of

aortitis develop 10 to 20 years after onset of disease in most cases, with the most common manifestation being a localized saccular aneurysm in the ascending aorta.[51]

## Inflammatory Aneurysms

Walker and colleagues[52] were the first to define the term *inflammatory aneurysm*. Typical histologic examination shows signs of chronic inflammation in the adventitia with a marked lymphoplasmacytic cell infiltrate and granulation or proliferation of fibrous tissue. Three inflammatory arteritides affect the ascending and arch of the aorta with aneurysmal disease: Takayasu arteritis, Behçet disease, and giant cell arteritis (GCA).

### TAKAYASU ARTERITIS

Takayasu arteritis is a nonspecific inflammatory disease of unknown etiology that mainly involves the medial layer in the elastic arteries such as the pulmonary artery, the subclavian artery, and abdominal branches of the aorta.[53] The inflammatory process results in a predominantly chronic arterial occlusive lesion of the main branches of the aortic arch but occasionally results in arterial aneurysmal formation, following a cyclic course.[54] Histologically, thickening of the intima is the normal occurrence, resulting in stenosis and occlusion; however, degeneration of the elastic tissue with proliferation of the connective tissue mainly in the medial layer of the arteries may result in dilatation of the artery and aneurysm formation.[54]

### BEHÇET DISEASE

Behçet disease is a multisystemic disorder characterized by recurrent urogenital ulcers, ocular manifestations, and skin lesions, with cardiovascular involvement appearing in only 7 to 29 percent of patients.[55] However, the leading cause of death in patients with Behçet disease is rupture of a large aortic or arterial aneurysm.[56] Venous lesions are the norm, with arterial manifestations accounting for only 12 percent of vascular complications in patients with Behçet disease. The arterial lesion, which develops in the aorta and the pulmonary artery as well as in their major branches, is an aneurysm in 65 percent of patients and an occlusion in 35 percent.[55] At histologic analysis, aortitis is seen in both the active and scar stages. Active aortitis leads to the destruction of the media and fibrosis, predisposing the patient to saccular aneurysms.[57] Perforation of the arterial wall caused by obliterative endarteritis of the vasa vasorum may result in aneurysm formation or rupture.[58]

### GIANT CELL ARTERITIS

GCA, also known as temporal arteritis, cranial arteritis, granulomatous arteritis, and Horton disease, is a chronic systemic vasculitis of unknown etiology that affects medium-size and large arteries.[59–61] It has been reported that as many as 15 percent of patients with temporal arteritis may have angiographic evidence of aortic involvement[62] and that patients with GCA are 17.3 times more likely to develop a thoracic aortic aneurysm than is the general population.[63] Typical histopathologic findings are disruption of the internal elastic lamina and an inflammatory cellular infiltrate with giant cells.[61]

## Complications of Ascending Aortic Dilation

Dilation of the ascending aorta is currently the most common cause of isolated aortic valvular regurgitation.[64] A normal valve becomes incompetent as a result of the passive stretching of its leaflets and commissures caused by dilation of the sinotubular ridge, the ascending aorta, or the sinuses, although the aortic annulus often remains normal in size in the non-Marfan population.

# CLINICAL FEATURES

The decision to recommend surgical therapy is based on the clinical assessment that the potential for complications during observation and the associated consequences are more significant than the morbidity and mortality of surgical repair. This clinical decision must rely on current knowledge of the natural history of ascending and arch aneurysms.

## Natural History

Unlike the natural history of untreated abdominal aortic aneurysms, the natural history of thoracic aortic aneurysms is ill defined, mainly because of the asymptomatic course of the disease until dissection, rupture, or the appearance of symptoms. The majority of the published information details the natural history of descending thoracic aneurysms, with substantially less information available for ascending or arch aneurysms. With that caveat, there is comprehensive information available for ascending and arch aneurysms related to MFS, but such data are lacking for other pathologies. It is appreciated that the size and etiology of the aneurysm contribute to the natural history of thoracic aortic aneurysms, which often concludes with patient death because of rupture or dissection.

### SIZE

According to Laplace law,

$$T = (P \times R)/M$$

where $T$ is the tension in the walls, $P$ is the pressure difference across the wall, $R$ is the radius of the cylinder, and $M$ is the thickness of the wall; the combination of an enlarging radius and a thinning wall leads to increased wall tension. This represents the onset of a positive feedback cycle that

results in progressive aortic dilation and culminates in rupture or dissection. In all reliable contemporary natural history studies, an ascending aortic diameter of 6 cm emerges as the mean or the median diameter quite consistently.[65] Coady and associates found that a diameter of 6 cm is the "hinge point" beyond which there is a 30 percent increase in the probability of rupture.[66] The 5-year survival rate for patients with ascending aortic aneurysms ranged from 36 to 61 percent in the earlier days[67] and reached 59 to 77 percent in the modern era[68] for aneurysms equal to or greater than 6 cm and less than 6 cm, respectively. Regarding aneurysm growth rates, Hirose and coauthors noted that the growth rate of aneurysms was greater in the arch (0.56 cm/year) than in the descending thoracic (0.42 cm/year) or the abdominal aorta (0.28 cm/year).[69] A more recent review of the Yale database[70] reported an annual growth rate of 0.07 cm for aneurysms in the ascending aorta or aortic arch and found that increasing size is associated more strongly with an increased risk of rupture than with an increased risk of dissection. In addition, the risk of rupture with time as a function of initial aneurysm size is 11 times worse with an aortic size of 5.0 to 5.9 cm and nearly 27 times worse with a size of 6.0 cm or greater when each is compared with aneurysms less than 4.0 cm.

### ETIOLOGY

In addition to aneurysm size, the etiology of the aneurysm has a profound impact on rupture, dissection, and death. The most common cardiovascular complication in patients with MFS is progressive aortic root enlargement that initially occurs at the sinuses of Valsalva. An ascending aortic aneurysm can precipitate acute type A dissection, aortic rupture, aortic regurgitation (AR), or all three, and these complications were the primary cause of death before the advent of successful preventive therapies.[2] Currently, aortic dissection is the major cause of premature morbidity and mortality in patients with MFS. In a study by Murdoch and associates,[71] that looked at causes of death in MFS patients, cardiovascular manifestations accounted for 93 percent of the deaths (52 of 56), with aortic root complications (dilation, dissection, and regurgitation) accounting for 80 percent of those deaths with an average age at death of 32 years. This was similar to the findings of Marsalese and coworkers, in which 87 percent of the known causes of death were attributable to the cardiovascular system and 61 percent were the result of aortic dissection, rupture, or sudden cardiac death with a mean age at death of 35 years.[72]

BAV is also an independent risk factor for progressive aortic dilation, aneurysm formation, and dissection.[73] Dore and associates[74] evaluated 50 adults with BAV with transthoracic echocardiography (TTE) and found that progressive dilation occurred at all levels (from the basal attachment of the leaflets to 1 cm beyond the STJ), ranging from 0.3 mm/year at the basal attachment within the left ventricular outflow tract to 1.0 mm/year 1 cm beyond the STJ. These rates of dilation are greater than the reported rate of 0.8 mm/decade in the normal population. In fact, BAV disease carries a 9-to-18-fold higher incidence of ascending aortic dilation.[75,76] Furthermore, valve replacement of BAV for either aortic insufficiency or stenosis does not eliminate the risk of aortic complications. After aortic valve replacement, BAV patients, when compared with tricuspid aortic valve patients, have progressive dilation of the proximal ascending aorta[77] and have a greater incidence of sudden death and aortic events.[78] Thus, the influence of BAV disease on the ascending aorta is a reality; surgeons should consider valve pathology when making decisions about ascending aortic replacement.

The natural history of LDS, resulting from a spectrum of mutations in *TGFBR1* or *TGFBR2*, differs considerably from other connective tissue disorders with the average age at the first cardiovascular event much lower than that for patients with untreated MFS or vascular EDS. In a cohort of 90 patients,[32] the median survival was 37.0 years, with 27 deaths during the study period with the mean age of death being 26.0 years (range: 0.5–47.0), and the mean age at vascular surgery—most often for ascending aortic aneurysm or dissection—was 19.8 years (range: 1.2–46.0). Twenty-nine patients (32 percent of the cohort) died before the age of 19 as a result of a vascular dissection or rupture, suggesting that LDS is an aggressive connective tissue disorder with a worse cardiovascular risk profile than classic MFS, including aortic dissection at a young age and at small dimensions.

## DIAGNOSTIC MODALITIES

### Typical Clinical Presentations

#### SYMPTOMS

Most patients with thoracic aortic aneurysms are asymptomatic at the time of presentation, and aneurysms of the ascending aorta usually are detected as incidental findings during testing for other disorders. Examples include widening of the mediastinum or prominence of the aortic knob on routine chest radiography and aortic enlargement on echocardiography, thoracic computed tomography (CT), or magnetic resonance imaging (MRI). In contrast, aneurysms of the aortic arch, because of their anatomic location and the space-occupying nature of the aneurysm, may impinge on important mediastinal structures and are therefore symptomatic more often than aneurysms of the ascending or descending thoracic aorta.[24] Hoarseness results from stretching of the left recurrent laryngeal nerve, stridor from compression of the trachea, dysphagia from impingement on the lumen of the esophagus, dyspnea from compression of the lung, and plethora and edema from compression of the superior vena cava (SVC).[79] Aneurysms of the ascending aorta associated with dilation of the aortic valve annulus may present with signs and symptoms of AR. In addition, chest or back pain may indicate acute expansion or leakage of the aneurysm in which the location of discomfort roughly correlates with the involved aortic

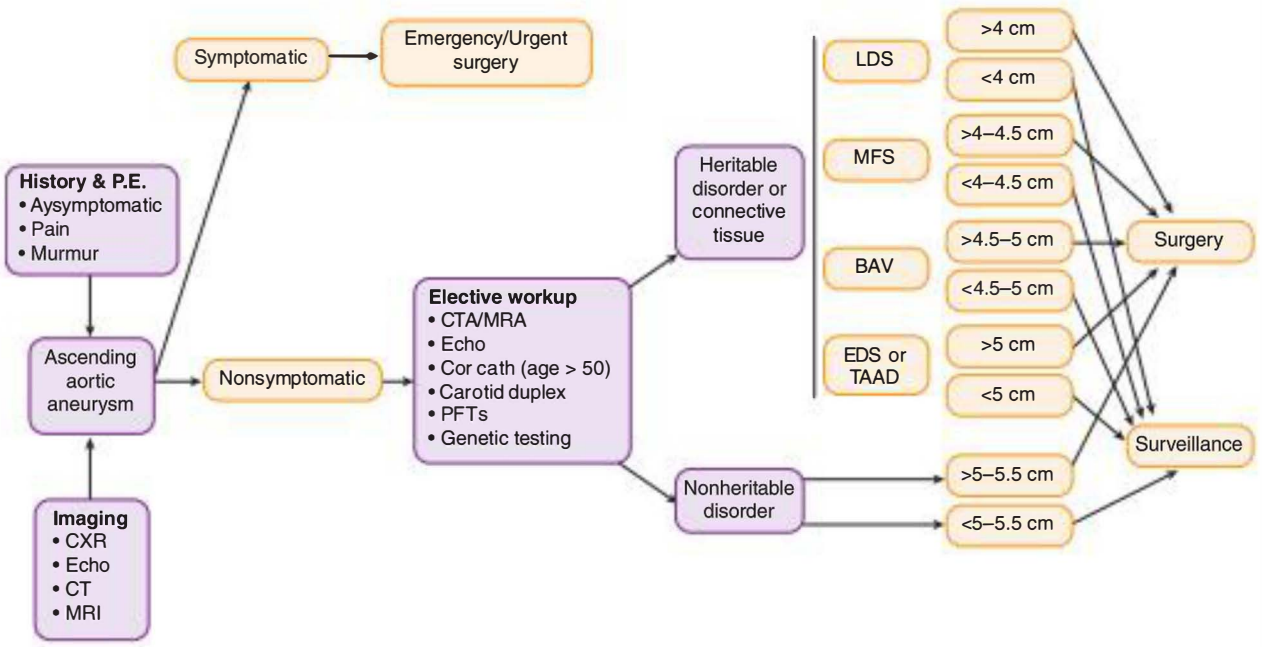



**FIGURE 39-7** Decision-making flowchart: ascending aortic aneurysm.

segment. Precordial pain is associated with involvement of the ascending aorta; radiation to the neck and jaw often accompanies aortic arch involvement, whereas descending thoracic and thoracoabdominal aortic aneurysms tend to produce interscapular and low back pain, respectively. In contrast, the clinical features of aortic dissection are the acute onset of chest and/or back pain of a blunt, severe, and sometimes radiating and migrating nature.[80] Symptoms attributable to the aneurysm are cause for concern and consideration for early surgical intervention. Patients with rupture of an ascending or arch aneurysm often present in extremis (see Figs. 39-7 and 39-8).

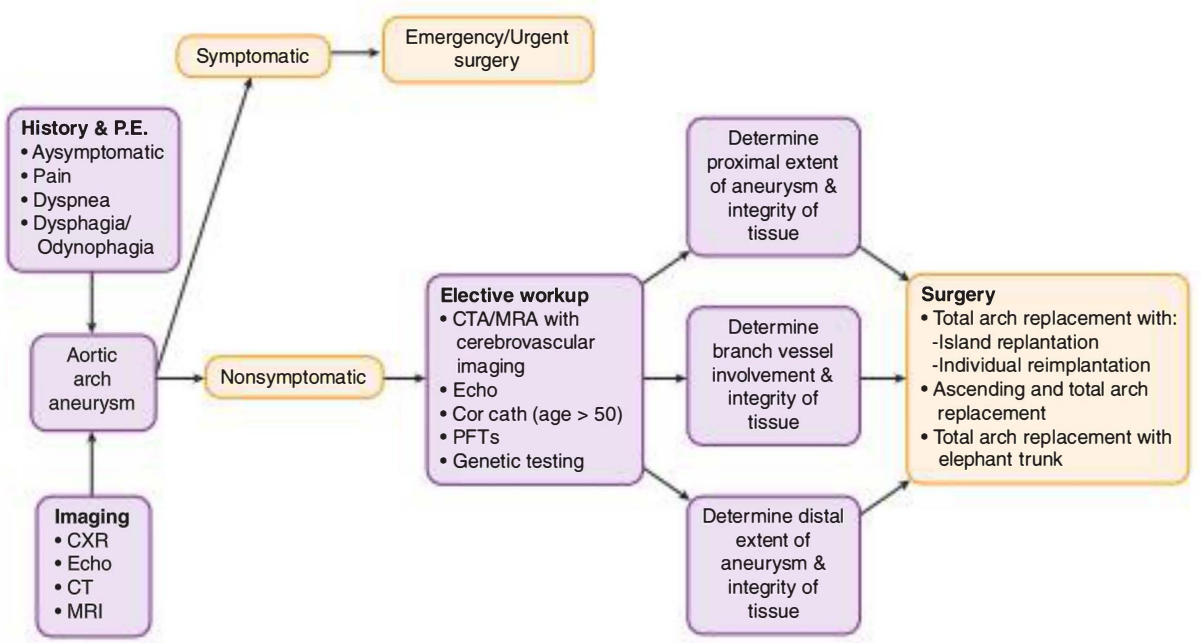



**FIGURE 39-8** Decision-making flowchart: aortic arch aneurysm.

### SIGNS

The physical examination is often normal in a patient without rupture of an ascending or arch aneurysm, with the rare exception of a large aneurysm that is palpated in the suprasternal notch. Other physical findings may include venous distention secondary to superior vena caval or innominate vein obstruction. Aneurysms of the ascending aorta associated with dilation of the aortic valve annulus may present with signs of AR (i.e., widened pulse pressure, decrescendo diastolic murmur, bisferiens pulse, "pistol-shot sound," Duroziez sign, and Quincke pulse). A thorough vascular examination should be carried out to identify concomitant peripheral vascular disease (abdominal aortic aneurysms are present in 10–20 percent of patients with atherosclerotic involvement of an ascending aortic aneurysm).[81,82] The physical examination also should focus on identifying marfanoid features (Fig. 39-4) as well as phenotypic features of LDS (i.e., blue sclerae, hypotelorism, bifid uvula, malar flattening, retrognathia, camptodactyly, arachnodactyly, and translucency of the skin with visible veins and distended scars[32]).

## Hallmark Primary Laboratory Abnormalities

There are no primary laboratory abnormalities associated with aortic aneurysmal disease.

## Recommended Diagnostic Studies

The diagnosis of aortic aneurysms has been revolutionized by developments in cross-sectional imaging. Traditionally, these aneurysms were investigated by contrast angiography, but the last two decades have seen considerable developments in the diagnosis of aortic disease by echocardiography, CT, and MRI. These developments have led to a complete change in the way in which aortic disease is evaluated and have contributed to an improvement in treatment outcomes.[83]

When a thoracic aortic aneurysm is detected, it is typically not possible to determine the rate of growth; therefore, if the aneurysm does not meet the criteria for surgical intervention, it is appropriate to obtain a repeat imaging study 6 months after the initial study. If the aneurysm is unchanged in size, it is reasonable to obtain an imaging study on an annual basis in most cases. However, if there is a significant increase in aortic size from one study to the next but surgical intervention is still not indicated, the interval between studies should be decreased to 3 or 6 months. For surveillance to be useful, serial imaging studies should be performed in the same center with the same technique so that direct comparisons can be made between comparable images.[50]

### CHEST ROENTGENOGRAPHY

The abnormality of a thoracic aneurysm may be detected on chest radiographs, with the most common finding being widening of the superior mediastinum. Other findings include displacement and compression of the mediastinal contents, such as the trachea and esophagus, and curvilinear calcification in the aneurysmal wall (Fig. 39-9).[84] However, aneurysms that involve the ascending aorta and the aortic arch sometimes cannot be differentiated from tumors or other masses in the mediastinum.[85]

### ECHOCARDIOGRAPHY

Both TTE and transesophageal echocardiography (TEE) play an important role in aortic imaging. Echocardiography is widely available, noninvasive (TTE) or minimally invasive (TEE), and relatively inexpensive. TTE can visualize the aortic root and ascending aorta accurately and is very suitable for evaluating the size of moderate aneurysms and assessing cardiac complications such as AR, impaired left ventricular function, and hemopericardium (Fig. 39-10). It is less than ideal for showing the full extent of the aortic arch and evaluating the origins of head and neck vessels. In contrast, TEE with the current multiplanar transducers has few blind areas (i.e., posterior to the trachea) that limit evaluation. Most important, because of its bedside applicability, TEE is the imaging modality of choice for the diagnosis and exclusion of ascending aortic dissection in an unstable patient, with a European multicenter study reporting a diagnostic sensitivity of 99 percent and a specificity of 98 percent.[86] Combined with color flow imaging, TEE allows not only the identification of the intimal flap with the true and the false lumen and identification of the entry and reentry tears but also the detection of associated complications such as AR, pericardial and pleural effusions, coronary involvement, and thrombosis in the false lumen. Today, in most centers, patients with proximal aortic dissection diagnosed by TEE who are surgical candidates are taken directly to the operating room, saving valuable time. In addition, intraoperative application of TEE allows continuous monitoring of the surgical procedure without disturbing the sterile field, in contrast to epicardial echocardiography.

### COMPUTED TOMOGRAPHY AND COMPUTED TOMOGRAPHY ANGIOGRAPHY

Because of its speed and wide availability, CT and computed tomographic angiography (CTA) are currently the most common diagnostic imaging methods for studying the aorta. With the advent of multidetector-row scanners, CT can provide the excellent spatial resolution necessary to image the aorta accurately with reasonable doses of iodinated contrast medium with a short acquisition time.[87] Limitations on contrast use because of renal insufficiency or a history of allergy usually can be dealt with, particularly when there is an urgent need to make a definitive diagnosis. CTA combines a rapid bolus intravenous injection using a pressure injector with a timed breath hold and spiral CT acquisition during peak arterial opacification. Curved planar reformations and three-dimensional (3-D) reformations using maximum-intensity projection (MIP) and shaded surface display (SSD) after segmentation and editing of bony and other unwanted

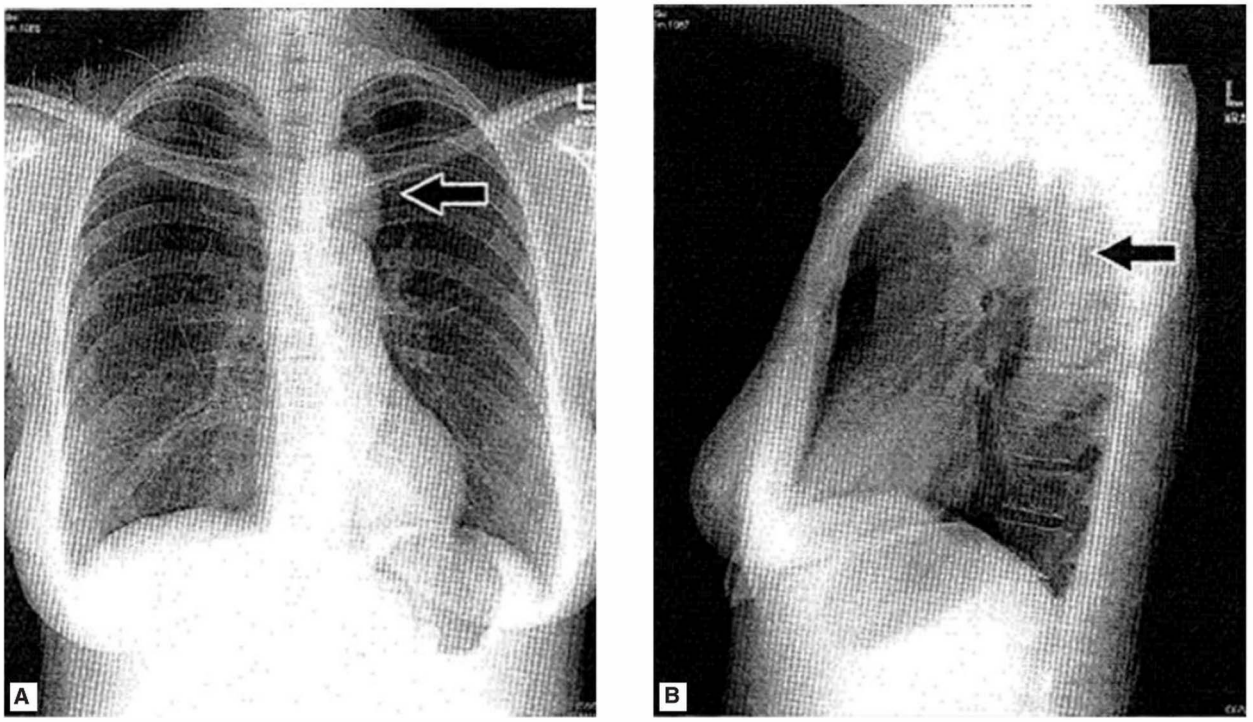



**FIGURE 39-9** Chest roentgenography demonstrating an aortic arch aneurysm (*black arrow*) on both the anterior–posterior film and the lateral film.

structures provide excellent visualization of the aorta and its branch vessels (Figs. 39-11 and 39-12).[88] CTA (axial images) has the advantage of demonstrating aortic wall thickening, calcification, and luminal thrombus, thus displaying the true axial extent of the aneurysm, as the aortography or 3-D MIP and SSD images display only the enhancing lumen of the vessel. In addition, these wall parameters are important in establishing the etiology of the aneurysm and in decision making for further management. However, it should be noted that measurement based purely on the basis of axial images, which may not be orthogonal, can be misleading. Tortuosity of the aorta can lead to a false estimation of aneurysm size; therefore, 3-D SSD reconstruction has facilitated assessment of aneurysm size and extent significantly.

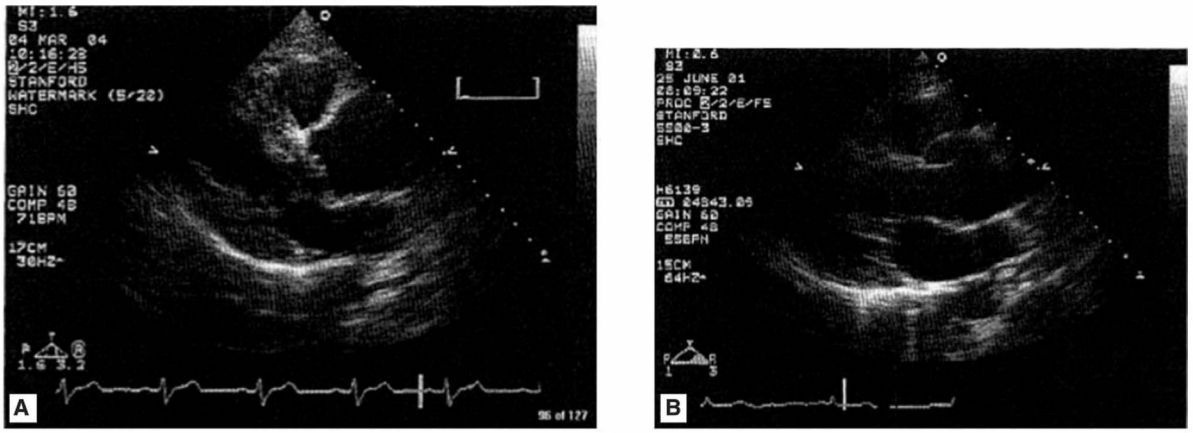



**FIGURE 39-10** Echocardiography. **A**. Long-axis view of a patient with a bicuspid aortic valve and an ascending aortic aneurysm. Note that the ascending aneurysm starts at the level of the sinotubular junction without dilation of the sinuses. **B**. In contrast, note the long-axis view of a Marfan disease patient with dilation of both the sinuses and the ascending aorta.

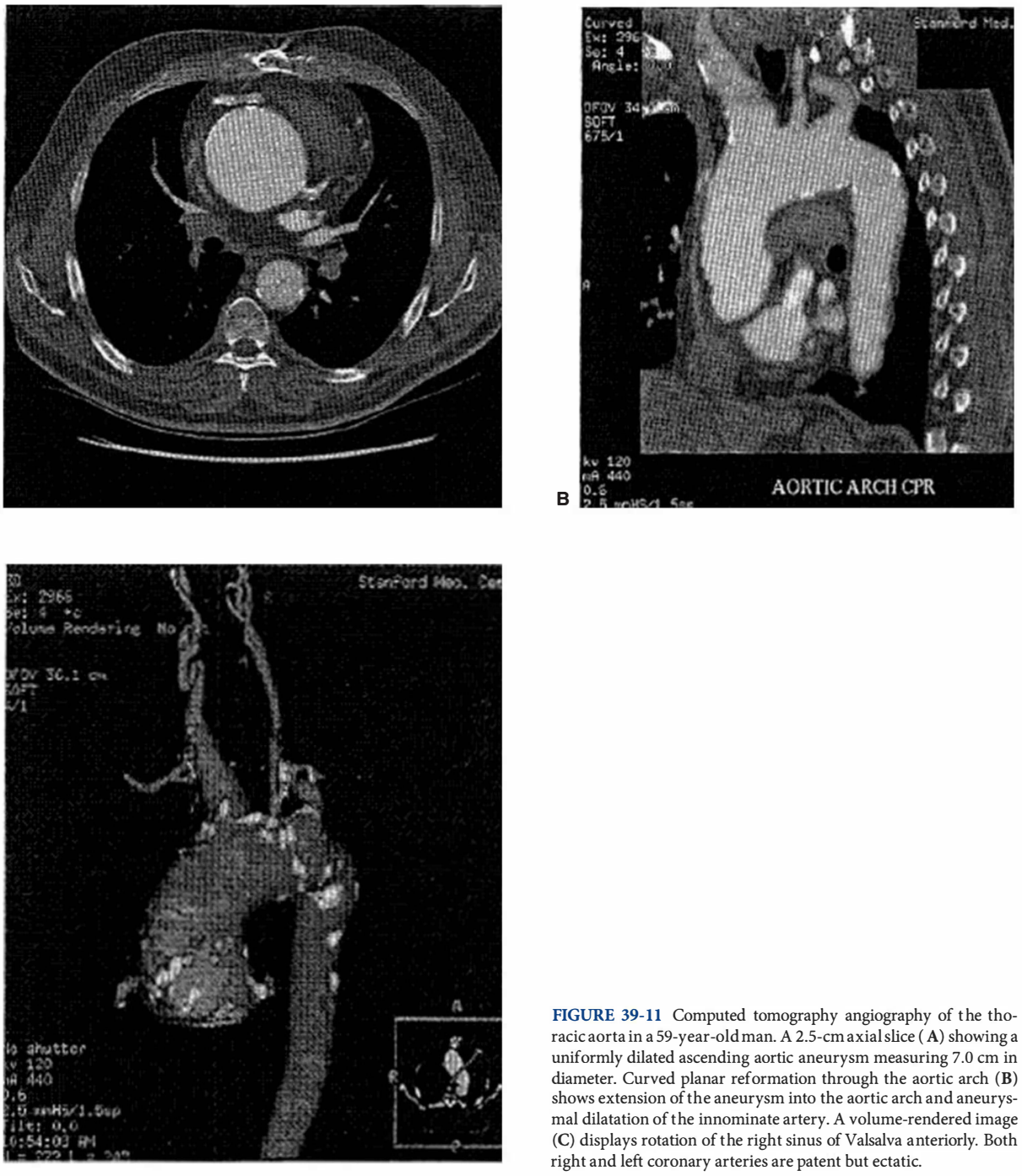



**FIGURE 39-11** Computed tomography angiography of the thoracic aorta in a 59-year-old man. A 2.5-cm axial slice (**A**) showing a uniformly dilated ascending aortic aneurysm measuring 7.0 cm in diameter. Curved planar reformation through the aortic arch (**B**) shows extension of the aneurysm into the aortic arch and aneurysmal dilatation of the innominate artery. A volume-rendered image (**C**) displays rotation of the right sinus of Valsalva anteriorly. Both right and left coronary arteries are patent but ectatic.

CTA is the imaging study of choice in a suspected leaking aneurysm, in which rapid evaluation is imperative. In elective ascending and arch aneurysm repair, CTA is able to display the origins of aortic branches and their relation to the aneurysm, the proximal and distal extent of the aneurysm, and the adjacent thoracic structures, all of which are critical to operative planning. Currently, 64-bit scanners also are capable of imaging coronary arteries, eliminating the necessity for selective catheter injection for coronary assessment.

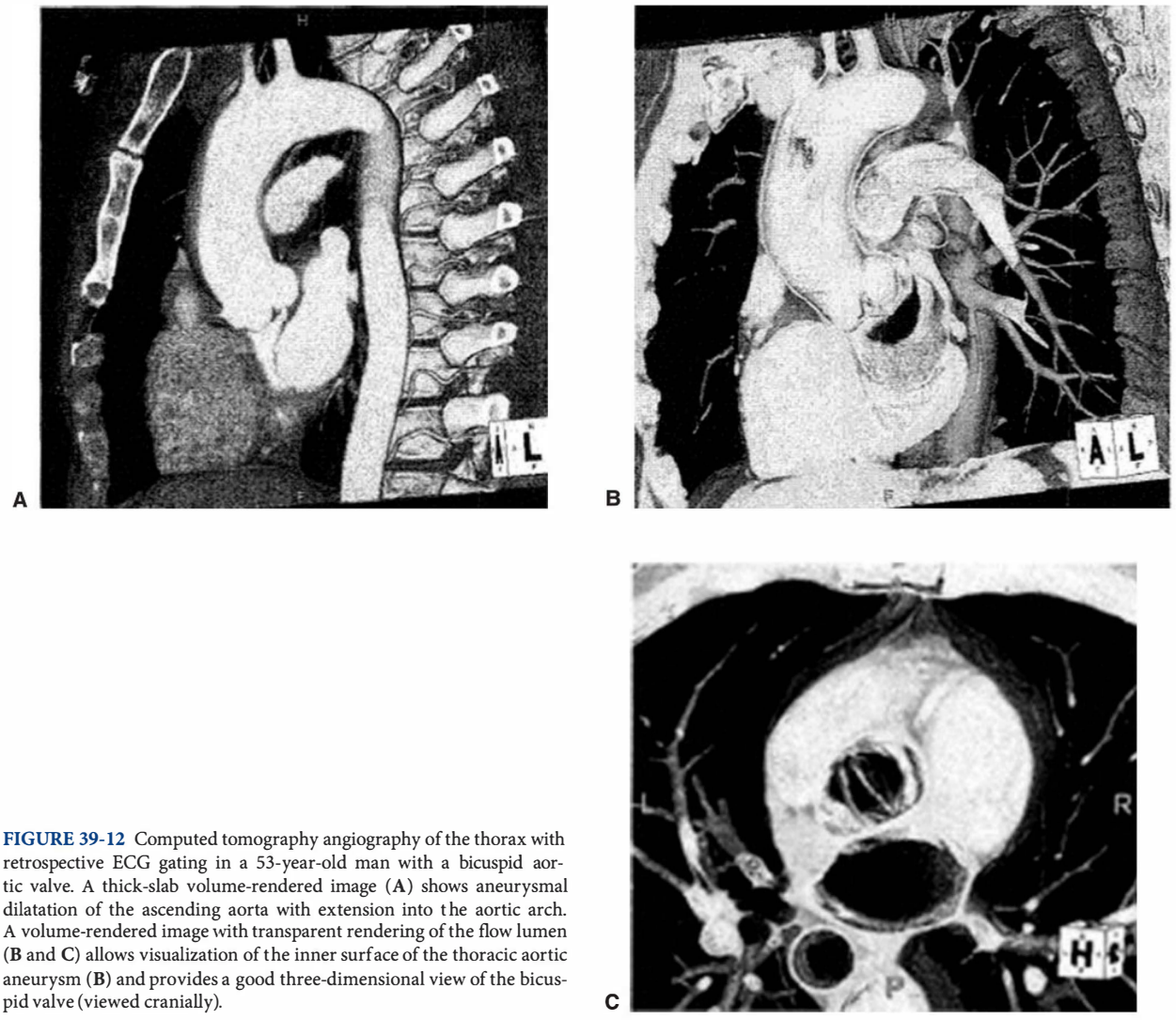



**FIGURE 39-12** Computed tomography angiography of the thorax with retrospective ECG gating in a 53-year-old man with a bicuspid aortic valve. A thick-slab volume-rendered image (**A**) shows aneurysmal dilatation of the ascending aorta with extension into the aortic arch. A volume-rendered image with transparent rendering of the flow lumen (**B** and **C**) allows visualization of the inner surface of the thoracic aortic aneurysm (**B**) and provides a good three-dimensional view of the bicuspid valve (viewed cranially).

### MAGNETIC RESONANCE IMAGING AND MAGNETIC RESONANCE ANGIOGRAPHY

MRI is emerging as the premier imaging method for the diagnosis of diseases of the thoracic aorta in stable patients. MRI provides visualization in the sagittal and coronal planes and eliminates the need for noniodinated contrast and radiation exposure. Magnetic resonance angiography (MRA) of the thoracic aorta usually requires a combination of several available MRI methods, each of which has certain advantages and contributes to the diagnostic versatility of the technique. Contrast-enhanced MRA (CE-MRA) is the most widely used MRA method because it is rapid and robust, providing projection images of the aorta similar to those provided by conventional invasive angiography. Black-blood MRI permits assessment of the vessel wall by saturating the signal from the lumen. Phase-contrast imaging provides functional information about the flow. Gradient-echo cine images can demonstrate AR in the presence of disease of the ascending aorta. The field continues to develop, and many new MRA methods promise further improvements in acquisition time and resolution.[89] However, MRI/MRA is less readily available and has limited utilization in acute aortic problems because of limited applicability to ventilated and invasively monitored patients. Indwelling pacemaker wires also frequently prevent its use.

## MEDICAL TREATMENT

The medical therapies available to slow the growth of thoracic aortic aneurysms and reduce their risk of dissection or rupture are quite limited, and most studies have focused

on Marfanoid patients. Whether these benefits truly can be extrapolated to the non-Marfan population with thoracic aneurysms is unknown.[50] Some early experimental evidence suggests that oxidative stress may play a role in the pathogenesis of atherosclerotic thoracic aortic aneurysms and that perhaps therapy with statins, MMP inhibitors, and angiotensin II receptor blockers may have a protective effect.[90,91]

## Marfan's Syndrome

Studies addressing the efficacy of β-blockade in MFS patients have concluded that such therapy is successful in a subset of individuals.[92,93] Overall, medicated patients showed slower aortic root growth (defined as absolute growth rate or growth rate adjusted for age and body size), fewer cardiovascular endpoints (defined as AR, dissection surgery, congestive heart failure, or death), and an improved survival rate.[2] It is important to note that even though abnormal aortic growth was slowed significantly in medicated patients, therapy did not prevent aortic dilation[94–96] or the need for surgical correction. Currently, it is recommended that all patients with MFS be considered for β-adrenergic blockade to reduce inotropy and chronotropy and thereby reduce both acute and chronic hemodynamic stress on the aortic root. Treatment begins with a low dose, which is titrated to keep the heart rate below 70 in a resting state and below 100 after submaximal exercise. Contraindications to β-adrenergic blockade include severe diabetes, Raynaud phenomenon, and bronchospasm. In the setting of β-blocker intolerance, a trial with a calcium channel blocker is indicated on the basis of a small trial that suggested its efficacy in protecting the MFS aorta.[93] Encouraging results in the Marfan rat model with angiotensin-converting enzyme (ACE) inhibitors may warrant a clinical trial.[97,98]

Exercise restriction represents a second approach to reducing hemodynamic stress in MFS patients.[99] Individuals with MFS are encouraged to remain active; aerobic exercise should be performed in moderation, but contact sports should be avoided. Most important, they should avoid isometric exercises, especially weight lifting, because of the marked elevation in blood pressure that occurs during sustained maximal muscle contraction.[2]

## Bicuspid Aortic Valve

The benefit of β-blockers in preventing aortic dilation in BAV disease is not clear; however, hypertension should be monitored and controlled carefully. The role of MMP inhibitors and gene or protein therapy in augmenting deficient extracellular matrix components in the bicuspid aorta is an exciting prospect that warrants further investigation.[100]

## Loeys–Dietz Syndrome

The mechanism by which mutations in the TGF-receptor cause the multisystem manifestations of LDS is complex and poorly understood. TGF-antagonists have the ability to alleviate or eliminate many manifestations, including aortic aneurysmsin mouse models of MFS.[101] Although the application of this approach to LDS may prove beneficial, caution is warranted pending validation in genetically defined animal models.[32]

# SURGICAL TREATMENT

The optimal timing of surgical repair of thoracic aortic aneurysms is somewhat uncertain in light of the limited data on their natural history.[50] The major objectives of surgical treatment are to alleviate symptoms related to the aortic disease, reduce the frequency of complications associated with the specific aortic disease, and, in the case of aortic aneurysm, prevent death from rupture. Extensive aortic disease may require staged operative procedures.[102]

## Indications for Operation

### SYMPTOMS

Symptomatic patients with ascending or arch aneurysms should be evaluated urgently for surgical repair. Patients presenting with rupture should be operated on urgently, since these conditions are almost uniformly fatal without prompt surgical intervention.

### SIZE AND GROWTH RATE

Current recommendations for elective resection of the ascending aorta are based on the fact that the mean diameter of the aorta at the time of dissection or rupture is around 6 cm, but this actually means that half of these patients have experienced a highly lethal complication by the time a diameter of 6 cm is reached.[103] Therefore, with the markedly reduced operative risk today, the authors, as do others,[104,105] recommend ascending aortic operations in nonheritable connective tissue disorder patients when the ascending aortic aneurysm diameter ranges from 5 to 5.5 cm. For patients who have diameters less than 5 cm and are being monitored with serial imaging, an indication for surgical intervention would be a 10 percent increase in size over a 6- to 12-month time course. In addition, since the majority of ascending aortic aneurysms are discovered in the course of evaluation for aortic insufficiency, progressive aortic valvular regurgitation is another common indication for operation.

### INFLUENCE OF ETIOLOGY

Patients with a heritable disorder of connective tissue such as MFS, EDS, LDS, BAV, or TAAD who have an ascending or arch aneurysm require earlier surgical intervention than do patients with nonheritable aortic disease. The traditional threshold that prompts the consideration of prophylactic aortic root replacement in patients with MFS has

been predicated on aortic size, and replacement is recommended when the diameter reaches 5.0 cm.[106,107] The association between increased aneurysm diameter and the risk for dissection or rupture has been established clearly, and aneurysm size greater than 6 cm portends a four-fold increase in the cumulative risk of aortic rupture or dissection in patients with MFS.[107] Some patients with MFS experience acute dissections when the aortic diameter is less than 5.0 cm.[108] In patients with LDS, aortic dissection often occurs in childhood and in aortas with diameters well under 5 cm.[32] Therefore, for heritable disorders of connective tissue, surgical intervention for the ascending aorta should be considered at a diameter approaching 4 cm for LDS patients, 4 to 4.5 cm for MFS patients, 4.5 to 5 cm for BAV patients, and 5 cm for EDS or TAAD patients. In addition, young children with LDS should undergo surgical intervention when the maximal dimension of the ascending aorta exceeds the 99th percentile and the diameter of the aortic annulus exceeds 1.8 cm.[32] For patients with ascending aortic aneurysms below these values, surveillance is warranted. Factors that prompt a recommendation for surgery when the aorta is less than 5.0 cm include rapid growth of the aortic diameter (more than 1 cm/year), a family history of premature aortic dissection (dissection less than 5.0 cm), and the presence of moderate or severe AR.[2]

## Choice of Operations

### ASCENDING AORTIC OPERATIONS

The surgical technique employed for treatment of an ascending aortic aneurysm varies with the underlying pathology and the quality of the aortic wall, the skill of the operating surgeon, the status of the aortic valve, and the age, expected survival, and general well-being of the patient.[23] The primary technical objectives of repair are surgical excision of all aneurysmal segments with graft replacement and restoration of function to the aortic valve.

Choosing the technique most appropriate for the patient and the pathology requires careful consideration of the factors that Ergin and associates[109] have outlined (Table 39-2). Among these factors are the following:

**TABLE 39-2: Factors Influencing the Choice of Ascending Aortic Operations**

| |
|---|
| Age and expected survival |
| Underlying pathology and quality of the aortic wall |
| Anatomic condition of aortic annulus, valve leaflets, sinuses, and sinotubular ridge |
| Condition of the distal aorta |
| Risk of anticoagulation |
| Presence of active annular infection |

Data from Ergin MA, Spielvogel D, Apaydin A, et al. Surgical treatment of the dilated ascending aorta: When and how? *Ann Thorac Surg* 1999;67(6): 1834–1839.

***Age and Expected Survival.*** In an older high-risk patient, separate valve and ascending aortic replacement may be the appropriate therapy if life expectancy is limited.[110] Reduction aortoplasty is less technically demanding than tube graft replacement of the ascending aorta, but the long-term results reveal a significant risk of recurrent dilation.[111,112]

***Underlying Pathology and Quality of the Aortic Wall.*** A weakened aortic wall in a patient with MFS or dissection will require complete excision of the dilated portion of the aorta and the root. The button modification of the Bentall procedure has proved in the authors' hands the most versatile and durable reconstruction.[113] Sparing the aortic valve in MFS patients is controversial,[114] although early data with 5-year follow-up is encouraging.

***Anatomic Condition of the Aortic Annulus, the Valve Leaflets, the Sinuses, and the Sinotubular Ridge.*** The anatomic condition of these important elements of aortic valvular integrity usually dictates whether the valve can be spared or whether a separate valve-ascending aortic replacement may be feasible. In the authors' experience, the ideal candidate for a valve-sparing root replacement is a patient with a normal valve and annulus in whom a dilated sinotubular ridge or dilated sinuses leads to aortic insufficiency. A separate valve and ascending aortic replacement that leaves behind thinned, dilated sinuses is a compromise that should be avoided in patients with a relatively long life expectancy.[115]

***Condition of the Distal Aorta.*** If the condition of the distal aorta mandates a future operation for associated distal arch or descending thoracic aortic aneurysm or dissection, a fail-safe initial repair at the root is of paramount importance. The presence of even modest degrees of AR may complicate an operation on the distal aorta substantially, and this frequently requires the utilization of hypothermic circulatory arrest. In these cases, the authors prefer a composite replacement rather than a valve-sparing procedure, except in the case of an absolutely normal valve with AR secondary to dilation of the STJ.

***The Risk of Anticoagulation.*** A young female desirous of child bearing presents a particularly challenging dilemma. A valve-sparing root repair or perhaps a pulmonary autograft may allow long-term durability. Reoperations on a biological CVG undoubtedly will incur more risk than will a simple aortic valve reoperation and should be avoided.

***Presence of Active Annular Infection.*** First and foremost, total excision of all infected tissue must be achieved. Annular and root reconstruction then can be accomplished with autologous materials, with the considerations for anticoagulation that were outlined above. Although low rates of reinfection may be achieved with conventional prostheses, repairs that avoid prosthetic material such as homografts and pulmonary autografts may be preferable.

### ARCH OPERATIONS

The specific technical aspects of aortic arch replacement depend on the location of the aneurysm within the arch and the extent of involvement of the contiguous ascending and descending thoracic aorta.[24] To replace the dilated arch with a prosthetic tube graft, the brachiocephalic vessels must be removed from the arch before its interposition. Traditionally, this involved removing and then reimplanting the brachiocephalic vessels en bloc during hypothermic circulatory arrest. However, many surgeons have adopted a newer surgical technique by using a multilimbed prosthetic arch graft to which each arch vessel is anastomosed individually in turn, thereby reducing the duration of hypothermic circulatory arrest; avoiding the proximal portion of the arch vessels, which is frequently diseased; and allowing inspection of all anastomoses for hemostasis.[50]

## Operative Technique

### PREOPERATIVE EVALUATION

Since myocardial infarction, respiratory failure, renal failure, and stroke are the principal causes of death and morbidity after operations on the thoracic aorta, preoperative assessment of the function of these organ systems is essential.[116]

### ANESTHETIC CONSIDERATIONS

Although the anesthetic management of patients undergoing aortic arch surgery includes practices common to most cardiac operations, there are conditions associated with the repair of aortic aneurysmal rupture that warrant special consideration. Anesthetic induction tends to blunt the sympathetically mediated compensatory responses of vasoconstriction and tachycardia that often are associated with acute thoracic aortic disruption. Therefore, acute cardiovascular collapse may result from conventional induction. To avoid this situation, endotracheal intubation and femoral vessel cannulation under local anesthesia with simultaneous institution of general anesthesia and CPB often are instituted in the setting of aneurysmal rupture.

***Standard Monitoring.*** After induction of anesthesia and intubation with a single-lumen endotracheal tube, venous access is obtained with a large-bore central line and several large-bore peripheral lines. For invasive arterial pressure monitoring and blood sampling, an arterial line is placed, but the location of placement is dependent on the operation that is being performed. If antegrade selective cerebral perfusion (ASCP) will be performed via the right axillary artery, the authors frequently monitor both left and right radial artery pressures. Pulmonary artery pressures, cardiac filling pressures, and cardiac output are measured by using a pulmonary artery catheter. Intraoperative TEE is used to estimate both ventricular filling and contractility, assess valvular function, allow selection of cannulation sites free of atherosclerotic disease, and confirm the appropriate advancement of the guidewire and venous cannula from the femoral vein into the SVC. Thermistor probes measure bladder, venous perfusate, and two tympanic temperatures. Five-lead electrocardiography and pulse oximetry are observed. Urine output is measured with a Foley catheter. Both invasive and noninvasive measures of cerebral oximetry also may be beneficial.

### PERFUSION

In the case of ascending aortic aneurysms, if an aneurysm does not involve the distal ascending aorta or the proximal aortic arch, these sites can be used for cannulation. If this is not possible, the axillary artery or innominate arteries may be used for arterial return from the pump-oxygenator. Femoral cannulation, especially in older patients with diffuse atheromatous disease, risks retrograde embolization to the brain as well as retrograde aortic dissection. Bicaval venous cannulation allows improved myocardial preservation as well as retrograde filling of the SVC as a final flush of particulate or gaseous material from the cerebral circulation before restoration of antegrade perfusion. In the case of arch aneurysms or if clamping of the ascending aorta is not possible, deep hypothermic circulatory arrest with additional cerebral protection is necessary.

### CEREBRAL PROTECTION

Because of its location, surgery of the aortic arch requires manipulation and exclusion of the cerebral circulation; therefore, cerebral protection is a primary concern and the utilization of optimal methods for the preservation of cerebral function is necessary to avoid ischemic or embolic brain injury. Over the past three decades, cerebral protection during arch procedures has evolved to avoid both the permanent and the transient neurologic dysfunction (TND) seen after aortic surgery. Initially, simple profound hypothermic circulatory arrest as described by Griepp and associates[17] seemed adequate, but it was associated with both focal and generalized neurologic injury with longer periods of arrest. Retrograde cerebral perfusion was popularized by Ueda and coworkers,[117] but TND was observed commonly with ischemic periods longer than 40 to 60 min. Selective antegrade cerebral perfusion and hypothermia as described by Kazui and colleagues[118] appears to provide cerebral protection for even longer ischemic periods (more than 40–60 min).

***Deep Hypothermia and Circulatory Arrest.*** The technique of deep hypothermia and circulatory arrest (DHCA) was described by Drew and associates in 1959.[119] Children undergoing surgery for Tetralogy of Fallot were cooled to 12°C (nasopharyngeal), allowing a circulatory arrest time of 1 h. The introduction of DHCA by Griepp and coworkers[17] as an operative tool more than 30 years ago still serves as the basis for the surgical treatment of complex thoracic aortic pathologies. This technique allows the performance of an open distal anastomosis and better visualization of the aortic

arch in a relatively bloodless field. The main disadvantages of DHCA include coagulopathy, increased CPB time, and renal and neurologic dysfunction.[120]

The vulnerability of the brain during circulatory arrest has been a great concern. Even at brain temperatures as low as 18°C, the safe arrest time is considered to be no longer than 30 to 40 min. An additional factor in the incidence of cerebral damage is the increasing age of these patients.[121] To protect the brain against ischemia, several different techniques are available, among which hypothermia is a standard, well-accepted application. To be able to establish the precise temperature of the brain, it is important to know which monitoring site is the most accurate for that purpose. The routinely used sites include esophageal, rectal, bladder, nasopharyngeal, pulmonary arterial, and skin temperatures. Several studies have compared the efficacy of the different monitoring sites in indicating the temperature of the brain, particularly in the dynamic phase of cooling and rewarming. Although core temperature sites, in particular bladder and esophageal temperature, may accurately reflect changes in body temperature during moderate hypothermia,[122,123] the accurate estimation of the optimal brain temperature site is still a matter of debate. The only available study in which brain temperature was measured directly during DHCA included patients undergoing surgical clipping of a cerebral aneurysm.[124] Routine monitoring sites, including tympanic temperatures, under- or overestimated brain temperature, with relatively large differences between individual patients. Although the effective time of arrest of cerebral perfusion has been shortened substantially by the application of antegrade low-flow cold blood cerebral perfusion, it is still important to assess cerebral temperature as accurately as possible. In the authors' practice at Stanford, this includes the measurement of bladder temperature, venous perfusate temperature, and two tympanic temperatures.

Since hypothermia is applied for brain protection because it diminishes cerebral oxygen consumption ($CMRO_2$), electroencephalography (EEG) monitoring has been advocated to assess uniform cooling and the degree of depression of the electrical signaling obtained during cooling. However, the EEG records only the postsynaptic potentials of cortical neurons, not the metabolic status of basal structures. During cooling, the EEG becomes isoelectric between 20°C and 18°C, but consistency of variation during hypothermia is unproven. The association between intraoperative EEG changes and postoperative neurologic deficits is weak. Still, EEG is used to determine electrical silence before DHCA and assess the effects of additional pharmacologic protective strategies.[125]

The bispectral index (BIS), which is derived from the analysis of phase and frequency interrelationships of EEG waves, was studied in patients undergoing cardiac surgery with CPB. BIS showed a reduced need for anesthetics after the initiation of CPB compared with before CPB.[126] This important observation was confirmed in patients by using the patient state index (PSI), another measure used to detect a patient's level of hypnosis.[127] Monitoring DHCA patients with PSI revealed that after rewarming and termination of CPB, the level of anesthetic sedation might last several hours without any additional administration of anesthetics. This might be due to the combination of deep hypothermia and pharmacologic protection with barbiturates, which is the authors' common practice. Since anesthetics may cause myocardial depression and unwanted hypotension as a result of vasodilatation, monitors such as BIS and PSI have the capacity to improve outcomes by preventing unnecessary anesthetic intervention in the early post-CPB period.

A second monitoring method to assess cerebral cooling and lowering of $CMRO_2$ that has been studied intensively is jugular venous bulb oxygen saturation ($SjVO_2$). $SjVO_2$ is measured by inserting a catheter percutaneously in the internal jugular vein and advancing it in a retrograde fashion into the jugular bulb. The actual measurements of $SjVO_2$ are performed intermittently by sampling from the catheter or continuously by using a fiber-optic catheter.[128] During cerebral cooling, the cerebral metabolic rate and cerebral oxygen extraction both decrease, resulting in an increase in $SjVO_2$. Some authors suggest that cooling during DHCA should continue until $SjVO_2$ has increased to at least 95 percent, indicating sufficient global cerebral hypothermia, although regional differences still will go undetected.[129]

The cerebral protective effect of hypothermia is undisputed,[130] but the specific temperature to guarantee maximal protection during DHCA is unknown. Hypothermia not only lowers the brain energy demands by lowering $CMRO_2$ but also provides protection by reducing excitatory neurotransmitter release, decreasing free radical production, and maintaining cellular integrity.[131] Most authors indicate that DHCA is started at a temperature of 15°C to 20°C measured at core, tympanic, or both sites.[121,132,133] The disadvantages of lower temperatures include fewer autoregulatory mechanisms and longer CPB times with resultant coagulopathies and cellular edema. Studies of neurologic deficit after DHCA conclude that an arrest time of 25 to 30 min is probably the maximally tolerated ischemic period, particularly for the brain. The duration of DHCA time and the age of the patients are reported to be the most important risk factors for mortality and postoperative neurologic deficit.[120,121,132]

To diminish cerebral ischemic time, perfusion of the brain during deep hypothermia has been implemented, including retrograde cerebral perfusion (RCP) and ASCP. Recent reports indicate the superiority of ASCP,[134–136] with neurologic deficit rates of 5 to 8 percent[132] and transient brain dysfunction rates of 10 to 30 percent.[120,135] Cerebral autoregulation is significantly better preserved with ASCP than with RCP or with no selective cerebral perfusion.[133] An alternative approach using the axillary artery for antegrade perfusion during DHCA has shown promising results[137] even in emergency conditions.[138] In addition, this technique of ASCP has allowed the recent trend away from very low temperatures toward higher systemic temperatures, up to 25°C with selective cold (15°C)[139,140] or even moderate hypothermic (25°C)[141] perfusion of the brain, to prevent temperature-induced coagulopathy and loss of cerebral autoregulation.

In spite of these improvements, the substantial residual neurologic problems after surgery with deep hypothermia have inspired researchers to focus on the rewarming phase after circulatory arrest. Several studies using $SjVO_2$ monitoring have reported significant venous desaturation during rewarming.[142,143] Apparently, there is a discrepancy between oxygen demand and oxygen supply in this crucial phase that was reported to be prevented by mild hypercapnia,[144] with a critical limit of desaturation defined as 50 percent.[142] Changing the rate of rewarming had no effect on the reduction of jugular venous saturation, indicating that a relative impairment of cerebral blood flow in the presence of marked hemodilution may be responsible for this phenomenon. Although there are no convincing data showing that jugular venous desaturation is related to postoperative neurologic deficit, a study using preoperative MRI suggested that patients with greater preoperative abnormalities had higher degrees of desaturation during rewarming.[145] Since patients undergoing surgery on the aortic arch may show preoperative impairment of cerebral perfusion, they represent a vulnerable group for venous jugular desaturation during rewarming after DHCA. Large, prospective multicenter studies may show a relationship between these two variables.

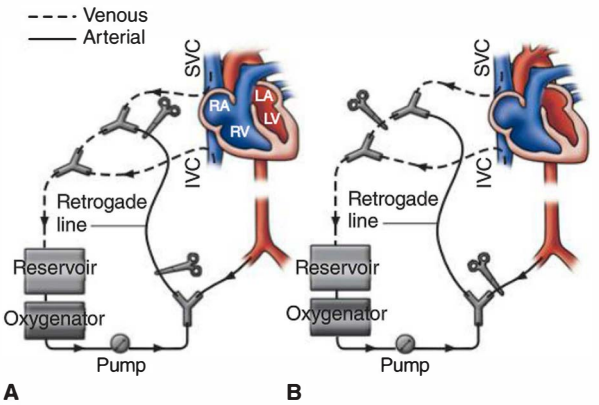



**FIGURE 39-13** Retrograde cerebral perfusion. Schematic for retrograde cerebral perfusion via the superior vena cava (SVC). **A.** Cannulation configuration for cardiopulmonary bypass and retrograde cerebral perfusion (RCP). The retrograde line is primed and clamped. **B.** RCP through the SVC after arterial return is directed through the retrograde line into the SVC. LA, left atrium; LV, left ventricle; RV, right ventricle; RA, right atrium; IVC, inferior vena cava.

***Retrograde Cerebral Perfusion.*** RCP was described by Mills and Ochsner in 1980 as a treatment for massive air embolism during CPB.[146] Intermittent and later continuous RCP was adopted by Ueda and associates[117] as a method for cerebral protection during procedures involving the aortic arch. Before the emergence of ASCP, RCP was used commonly as an adjunct to DHCA during surgery on the thoracic aorta as a way to improve neurologic outcomes. In RCP, oxygenated blood is delivered to the brain in a retrograde manner via a cannula placed in the SVC (Fig. 39-13). The hypothetical neuroprotective mechanisms of RCP include maintenance of cerebral hypothermia, washout of embolic air or debris, cerebral perfusion, and metabolic support. However, on the basis of human and laboratory investigations, the neuroprotective mechanisms of RCP remain controversial. Compared with ASCP, RCP seems to be less effective but still provides somewhat more brain preservation than does DHCA, probably as a result of the continued cerebral cooling via the venoarterial and venovenous collateral circulations.[147]

***Antegrade Selective Cerebral Perfusion.*** The earliest attempts to repair the aortic arch relied on complex methods of extracorporeal cerebral perfusion. In 1957, DeBakey and associates[15] reported a successful resection of an aortic arch aneurysm using normothermic CPB achieved by means of several pumps and bilateral cannulation of both the subclavian and carotid arteries. Eventually, the CPB perfusion technique was simplified by Dubost and associates[148] and Pearce and associates[149] by using a single pump with a Y-connection of the arterial line; however, over the next two decades, extracorporeal cerebral perfusion during aortic arch replacement was overshadowed by the growing interest in and utilization of circulatory arrest and deep hypothermia.[147]

In 1986, Frist and associates[150] from Stanford initiated the new ASCP "era" by incorporating a CPB technique with partial brachiocephalic perfusion, with low CPB flow (30 to 50 mL/kg/min) and moderate systemic cooling (26°C–28°C).[147] The arterial line from a single pump head had a Y-shape to perfuse both the femoral artery and either the innominate or the left carotid artery. In 1991, Bachet and associates[151] introduced a procedure that employed cold blood "cerebroplegia," which was perfused via the innominate and left common carotid arteries through separate pumps and heat exchangers. Kazui and colleagues[118] are credited with advancing the current use of ASCP by introducing the employment of separate arterial pump heads for the cerebral and systemic circulations to provide individual hypothermic perfusion to each system at 25°C (Fig. 39-14). Cerebral perfusion was achieved by means of endoluminal cannulation of the brachiocephalic and left common carotid arteries while the left subclavian artery was clamped or occluded with a Fogarty catheter to avoid the steal phenomenon. In an elegant experimental study, Tanaka and associates[152] provided laboratory evidence supporting the use of ASCP and outlined important perfusion details such as the optimum perfusion flow rate, pressure, and temperature.

***Pharmacologic Protection.*** Because deep hypothermia, including ASCP, often leads to an unwanted neurologic outcome in patients with circulatory arrest, additional strategies of neuroprotection are applied, including pharmacologic interventions. The cerebral protective effects of barbiturates in global ischemia have been studied in various models, including in humans after cardiac arrest.[153] All the trials failed to demonstrate an improvement in outcome. There are no randomized clinical studies showing advantageous effects

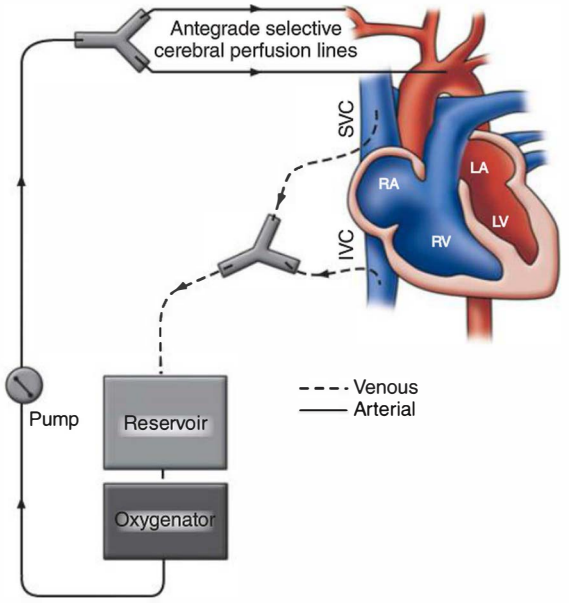



**FIGURE 39-14** Antegrade cerebral perfusion. Schematic for antegrade selective cerebral perfusion via the right axillary artery and the left common carotid artery. LA, left atrium; LV, left ventricle; RV, right ventricle; RA, right atrium; IVC, inferior vena cava.

of barbiturates in DHCA patients, and it has been suggested that barbiturates may jeopardize the energy state of the brain in patients with these conditions.[154] Still, in a survey on current practice, 35 percent of the respondents believed there was sufficient evidence to support the use of barbiturates in aortic surgery with DHCA.[155] As potential support for the use of barbiturates, it could be stated that barbiturates have been shown to be protective in patients with incomplete, focal ischemia in specific settings such as those which are present during CPB because of multiple emboli. In addition, they may be helpful in protecting the brain during rewarming after DHCA, particularly in the early phase, when the observed jugular venous oxygen desaturation mentioned above indicates a lack of oxygen delivery.

Steroids, in particular dexamethasone and methylprednisolone, are used routinely during DHCA surgery,[155] mainly because they counteract the systemic inflammatory response (SIRS) during and after CPB. Brain ischemia is considered to be a combination of embolization and SIRS, and steroids have been shown to improve the neurologic outcome in DHCA patients.[156]

## SPECIFIC OPERATIVE CONSIDERATIONS

***Replacement of the Ascending Aorta.*** Once stable CPB has been established, left heart venting is accomplished through either a pulmonary artery vent or a right superior pulmonary venous vent (Fig. 39-15). A balloon-tipped catheter is inserted into the right atrium and positioned in the coronary sinus for the delivery of retrograde cardioplegia. Adjunctive $CO_2$ perfusion of the operative field may be used. After myocardial protection is assured by instituting intermittent cold coronary sinus perfusion plus topical hypothermia, the ascending aorta is cross-clamped proximal to the origin of the innominate artery. The aorta then is transected proximal to the aortic clamp (leaving a cuff of circumferential aortic tissue to suture) and at the STJ. A Dacron tube graft that is selected to match the diameter of the aorta is anastomosed end to end to the distal aortic cuff with running 4-0 polypropylene sutures, commencing on the left side, passing along the posterior wall to the right, and being completed along the anterior wall. If the aortic wall integrity is suspect, a 4- to 5-mm strip of polytetrafluoroethylene (PTFE) felt may be incorporated in the distal suture line to minimize blood loss from suture pull-through. If aortic valve replacement or repair is necessary, it is performed. The proximal anastomosis then is performed by trimming the tube graft at the appropriate length, followed by suturing to the proximal aorta with a 4-0 polypropylene suture. Once again, if aortic wall integrity is suspect, incorporation of PTFE felt for reinforcement is recommended. Just before completion of the proximal anastomosis, the pulmonary artery vent is

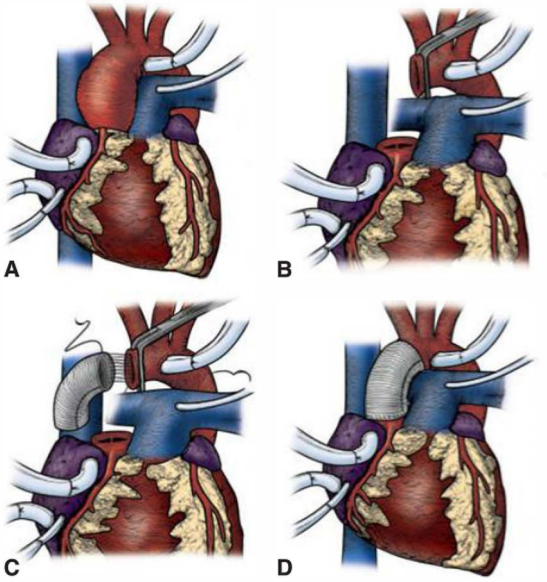



**FIGURE 39-15** Ascending aortic replacement. **A.** Routine cannulation with arterial cannulation in the underside of the midarch. Bicaval cannulation and retrograde cardioplegia are used, as well as a pulmonary artery vent. **B.** After cross-clamping the aorta and instilling cardioplegia, the aortic valve, sinuses of Valsalva, coronary ostia, and sinotubular junction are all ascertained to be normal. **C.** Full-thickness cuffs of proximal and distal aorta are fashioned, and then an end-to-end anastomosis with an appropriately sized woven Dacron graft is constructed, utilizing running 4-0 monofilament sutures. **D.** An aspirating needle in the highest point of the graft allows evacuation of air before discontinuation of the bypass. (Illustration by Simon Kimm, MD.)

discontinued, the heart is filled with blood, and standard de-airing procedures are carried out. The proximal suture line then is tied; a needle vent is placed in the graft and connected to cardiotomy suction to expel any residual air with the patient in the Trendelenburg position. Finally, the aortic crossclamp is removed from the graft, allowing reperfusion of the coronary circulation. Strict attention is paid to avoiding left ventricular dilation until cardiac ejection commences. Once rewarming has been completed, CPB is terminated, followed by removal of cannulas and the achievement of hemostasis. Hemorrhage can be a serious problem after repair despite meticulous surgical technique. Consequently, the application of local hemostatic factors (e.g., thrombin-impregnated Gelfoam, Avitene, or Surgicel) in addition to the appropriate administration of procoagulant factors is often necessary.

***Replacement of the Ascending Aorta and Aortic Root.*** Once stable CPB has been established, a left heart vent is placed and a balloon-tipped catheter is inserted into the right atrium and positioned in the coronary sinus for the delivery of retrograde cardioplegia (Fig. 39-16). After the aorta is cross-clamped proximal to the origin of the innominate artery, the myocardial preservation techniques that were described previously are instituted. The aorta is completely transected proximal to the aortic clamp (leaving a cuff of circumferential aortic tissue to suture) and just above the level of the main coronary artery ostia. The aortic valve then is excised, and a CVG repair commences. For a mechanical valve, a Dacron valved conduit is sutured into the annulus with 2-0 pledgeted horizontal mattress sutures. For a biological valve, a porcine root replacement is instituted with interrupted 3-0 horizontal mattress sutures. The left and right coronary artery orifices are excised from the aorta, leaving a 4- to 5-mm rim of aortic wall. Approximately 1 to 2 cm of the coronary arteries are mobilized carefully to avoid tension; the left coronary button is anastomosed to the valved conduit, using a running 5-0 polypropylene suture. To avoid traction and subsequent distortion of the right coronary artery, the distal graft anastomosis is completed before the right coronary button anastomosis is performed. Therefore, the valve conduit is measured, transected, and sutured end to end to the distal aorta with a running 4-0 polypropylene suture and allowed to fill retrograde, followed by the right coronary button anastomosis. Just before the completion of this suture line, the heart is filled with blood and standard de-airing maneuvers are performed. A needle vent connected to cardiotomy suction is placed in the graft, and any residual air is expelled with the patient in the Trendelenburg position. Finally, the aortic crossclamp is removed from the graft, allowing reperfusion of the coronary circulation. Once rewarming has been completed, CPB is terminated, followed by removal of the cannulas and achievement of hemostasis.

***Replacement of the Ascending Aorta and Aortic Root with a Homograft or Xenograft.*** In patients with infective endocarditis and aortic root dilation, homograft aortic root replacement is a good option after radical debridement of all infected or devitalized tissue. The proximal end of the graft is sutured to the native aortic annulus with interrupted or continuous 4-0 polypropylene sutures. Occasionally, the suture line is reinforced with a strip of pericardium to ensure hemostasis and the aortic homograft is placed in the natural position without rotation. The homograft anterior mitral valve leaflet can be utilized to patch erosions into the septum after meticulous debridement. Anastomoses are then created between the native left and right coronary artery ostia and the corresponding coronary ostia of the aortic homograft. Extension with a Dacron tube graft sometimes is used to replace the entire diseased aorta. For implantation of a xenograft, refer to Chapter 32.

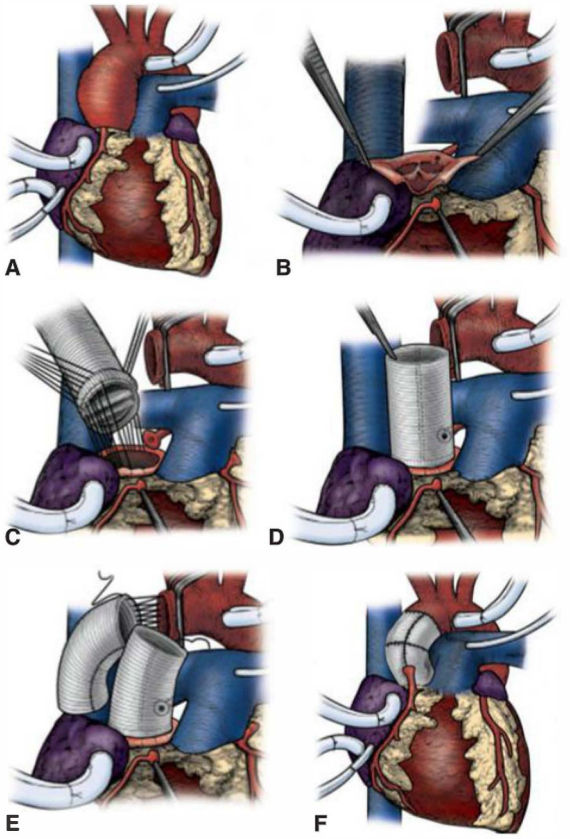



**FIGURE 39-16** Replacement of ascending aorta and aortic root. **A.** An ascending aortic aneurysm that involves the sinuses of Valsalva. Cannulation is as in Figure 35-13, but because of aortic regurgitation, antegrade cardioplegia is delivered via a hand-held cannula. **B.** The dilated coronary sinuses along with the diseased aortic valve are excised. **C.** A composite valve graft is then sewn with interrupted, everting pledgeted 2-0 mattress sutures to the aortic annulus. **D.** Full-thickness coronary buttons are fashioned, with the left button reimplanted first. **E.** The distal anastomosis with a running 4-0 polypropylene suture, utilizing a separate graft, which allows an end-to-end Dacron anastomosis using different size grafting materials for the proximal and distal anastomosis. **F.** The repair is complete after the graft-to-graft anastomosis, and a tension-free reimplantation of the right coronary button is performed. (Illustration by Simon Kimm, MD.)

**TABLE 39-3: Techniques for Reestablishing Coronary Flow in Ascending Aortic Aneurysms**

| Technique | Description |
|---|---|
| Classic Cabrol | Two coronary ostia connected in an end-to-end fashion with Dacron interposition graft, which is then anastomosed side to side with the aortic conduit |
| Modified Cabrol | Coronary ostial buttons are mobilized, sutured end to end with a smaller Dacron tube graft, and then anastomosed side to side with the aortic conduit |
| Kay–Zubiate | Individual coronary button anastomosed end to end with an interposition graft of autologous vein, then an end-to-side anastomosis with the aortic conduit |
| Dacron interposition | Individual coronary button anastomosed end to end with an interposition graft of Dacron, then end-to-side anastomosis with the aortic conduit |

***Reestablishing Coronary Flow.*** Frequently, with large aneurysms or false aneurysms, the coronary ostia are laterally displaced from the new aortic lumen. This distance can make primary attachment of the coronary ostia to ascending graft difficult even after adequate mobilization with full-thickness aortic buttons, especially in reoperative patients. Therefore, coronary flow can be established with various techniques (Table 39-3 and Fig. 39-17). Cabrol and coworkers[157] originally described connecting the two coronary ostia end-to-end with a separate Dacron interposition graft that then was anastomosed side-to-side to the aortic conduit; the entire repair was wrapped in the aneurysm wall to control bleeding. The modified Cabrol technique involves resecting the entire aortic wall and forming coronary ostial buttons, which are mobilized, sutured end-to-end with a smaller Dacron tube graft, and anastomosed side-to-side with the aortic conduit.[158] Alternatively, the Kay–Zubiate technique[159] relies solely on autologous tissue; saphenous vein is employed as an interposition graft for the displaced coronary ostia. In the absence of infection and particularly in reoperative aortic root operations in which adequate mobilization of the coronary buttons is impossible, a short interposed segment of a 6- or 8-mm Dacron™ graft works nicely.

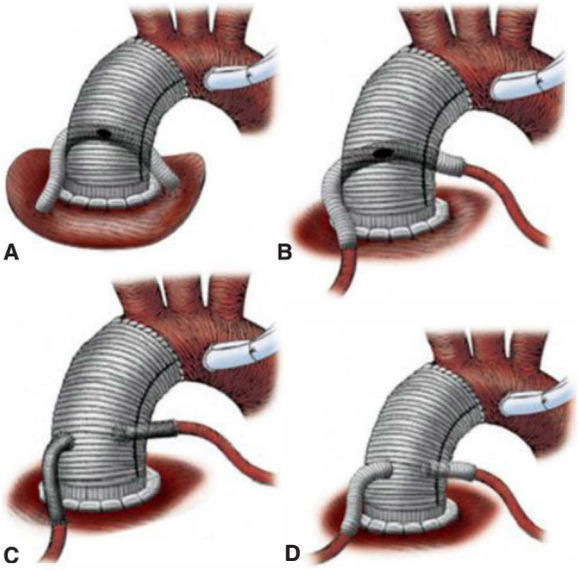



**FIGURE 39-17** Alternative methods for coronary reimplantation. **A.** The classic Cabrol method, with a 6- or 8-mm graft sewn end-to-end to the coronary ostia and side-to-side to the aortic graft. **B.** Cabrol modification that utilizes the same graft sewn end to end to full-thickness coronary buttons, again with a side-to-side central anastomosis. **C.** Using short segments of saphenous vein graft to sew end-to-end to full-thickness coronary buttons to allow revascularizing coronaries that are laterally displaced that cannot be mobilized back toward the aortic graft. **D.** An alternative utilizing 6-mm Dacron conduit as an interposition graft. (Illustration by Simon Kimm, MD.)

***Axillary Artery Cannulation.*** The axillary and innominate arteries are our preferred site of arterial cannulation for CPB when either the ascending aorta or the arch is unsuitable for cannulation and/or to facilitate selective antegrade cerebral perfusion when hypothermic circulatory arrest will be utilized in the performance of an open distal anastomosis (Fig. 39-18). The technique begins with a 6- to 8-cm transverse incision approximately two fingerbreadths below the distal clavicle in the deltopectoral groove. The pectoralis major muscle is divided in the direction of its fibers. The pectoralis minor muscle is retracted laterally or divided. Using sharp dissection, the artery is dissected from the surrounding tissue. Because the axillary artery lies deep to the axillary vein, it is usually necessary to mobilize and retract the vein. Care is taken to preserve elements of the brachial plexus or to avoid disrupting lymphatics, especially in females. Proximal and distal control of the axillary artery is obtained, and 5000 units of heparin is administered intravenously. A longitudinal arteriotomy is performed, and a 6- or 8-mm Dacron side graft is anastomosed end-to-side to the axillary artery with 5-0 polypropylene suture. The vascular clamps are removed from the artery, restoring flow to the right arm, and the Dacron graft is filled with heparinized saline solution. A 3/8″-1/4″ connector is inserted into the graft, secured with heavy ligatures, and connected to the CPB circuit. At the termination of CPB, the graft is amputated just proximal to the anastomosis, leaving a 2- to 3-mm cuff that is oversewn with

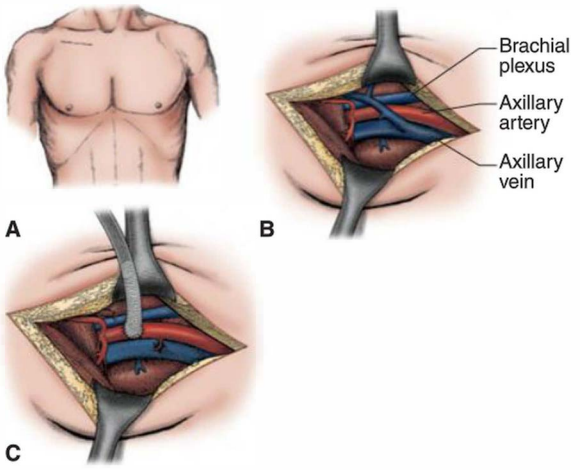



**FIGURE 39-18** Axillary artery cannulation. **A.** Infraclavicular incision on the right in the deltopectoral groove. **B.** Axillary artery is dissected from behind the overlying axillary vein, which then is clamped with a partially occluding side-biting clamp, allowing an end-to-side anastomosis with a 6- or 8-mm Dacron graft (**C**). This graft then can be cannulated for an arterial cannulation site. (Illustration by Simon Kimm, MD.)

a double layer of 5-0 polypropylene suture. The clavipectoral fascia, subcutaneous tissue, and skin are closed in three separate layers with a running absorbable suture.

***Open Distal Anastomosis and Replacement of the Aortic Arch.*** The open technique to create the distal anastomosis is required when aortic arch or hemiarch reconstruction is indicated. Upon completion of axillary artery cannulation, midline sternotomy, mediastinal dissection (including exposure of the proximal innominate artery and left carotid artery), and venous cannulation (bicaval, two stage, or femoral) are performed. The patient is cooled systemically to a target temperature of approximately 22°C. In the interim, the ascending aorta is fully mobilized and cross-clamped distally. An aortotomy is performed to decompress the aneurysm proximally and a diastolic arrest of the heart is induced by using cold blood cardioplegia via antegrade, retrograde, and/or handheld ostial delivery in concert with topical hypothermia. The aortic root is dissected further with excision/debridement of aortic valvular elements and dissection/mobilization of the coronary buttons. Replacement of the aortic root and reimplantation of the coronary buttons may proceed at this point or be deferred, based on when systemic cooling is complete. When the target temperature is achieved, the patient is placed in the Trendelenburg position and the innominate artery is clamped proximally, arresting flow to the body and permitting selective antegrade cerebral perfusion via the right common carotid artery and the right vertebral artery to proceed at a flow rate of 5 mL/kg/min. The aortic crossclamp is removed, and diseased distal ascending and aortic arch tissue is excised. Back bleeding through the left common carotid may be absent, suggesting an incomplete circle of Willis, or may be present but falsely reassuring if it is derived from collateral flow via the external carotid system. Therefore, to enhance antegrade cerebral perfusion, an appropriately sized pediatric coronary sinus catheter is placed into the left carotid artery via its takeoff from the aortic arch, secured in place by insufflation of the balloon cuff, and further bolstered by an extrinsic Silastic vessel loop. The loop is connected to the arterial inflow, providing an additional source of antegrade cerebral perfusion at 5 mL/kg/min. Higher cerebral temperatures may require selective antegrade cerebral blood flows of up to 20 mL/kg/min.

Depending on the integrity and caliber of the ostia of the great vessels, they may be reimplanted together as an "island" (Fig. 39-19A) or a "peninsula" (transverse arch or hemiarch replacement; Fig. 39-19B) as well as individually (in the setting of total aortic arch replacement). If chronic dissection is present, the septum between the true and false channels of the descending thoracic aorta is excised, providing a common channel. For total aortic arch replacement, it is often convenient to utilize a prefabricated branch graft, which may provide enhanced flexibility and efficiency in configuring the arch reconstruction (Fig. 39-19C). In any event, the distal

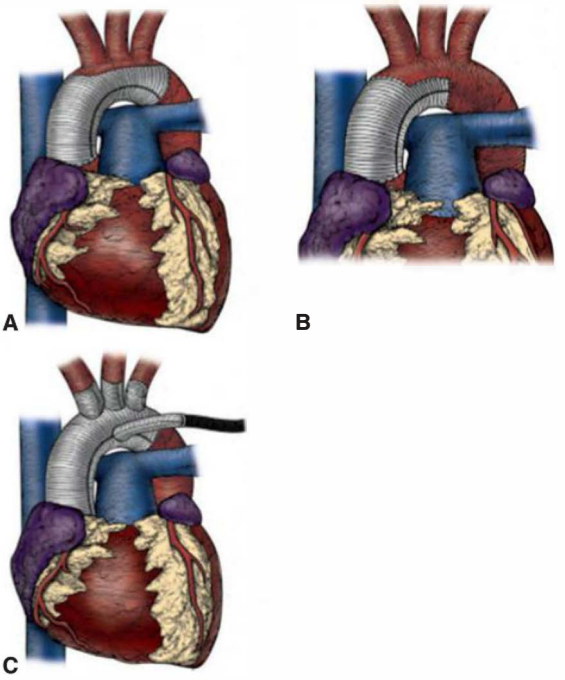



**FIGURE 39-19** Multiple methods for aortic arch reconstructions. **A.** A complete arch replacement with distal end-to-end anastomosis and reimplantation of left subclavian, left common carotid, and innominate arteries as an "island" patch. **B.** The hemiarch or "peninsula" technique. **C.** An alternative method utilizing a multibranch graft with individual anastomoses to the left subclavian, left carotid, and innominate arteries, utilizing the fourth branch as a perfusion port. (Illustration by Simon Kimm, MD.)

aortic anastomosis is constructed by using a felt reinforced 4-0 polypropylene suture technique. Great vessel reimplantation is performed with a 6-0 polypropylene running suture. After completion of the arch anastomoses, antegrade flow into the graft is commenced and gradual rewarming is initiated while the proximal aortic reconstruction is completed.

In the setting of known descending thoracic aortic disease that is likely to require future operative repair, an "elephant trunk" distal aortic repair should be utilized (Fig. 39-20). In this technique, a 5- to 10-cm cuff of Dacron graft is left in the native descending thoracic aorta to provide a proximal anastomotic site for future intervention (open repair via left thoracotomy or stent graft via an endoluminal approach). An appropriately sized Dacron tube graft is chosen. Stay sutures are placed on the proximal extent, which is intussuscepted into the distal portion of the graft destined to serve as the elephant trunk. The graft in this intussuscepted configuration is inserted into the distal aorta, and a running 4-0 polypropylene anastomosis is fashioned between the native aorta and the indwelling double-layer tube graft. The intussuscepted proximal portion of the tube graft is retrieved from the descending thoracic aorta by placing traction on the previously placed stay sutures. The remainder of the aortic arch reconstruction proceeds as described previously.

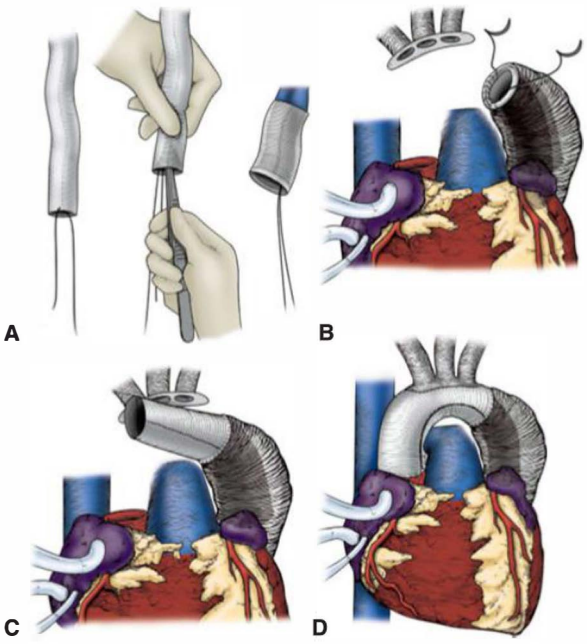



**FIGURE 39-20** Complete arch replacement utilizing the elephant trunk technique. Initially, an appropriate-length graft is intussuscepted into itself (**A**) and then placed into the proximal descending thoracic aortic aneurysm, and the distal anastomosis is constructed to full-thickness aorta (**B**). The arch part of the graft then is withdrawn from the elephant trunk, and the arch vessels are reanastomosed in the preferred manner (**C** and **D**). This method facilitates subsequent operations, as necessary, on the descending thoracic aorta. (Illustration by Simon Kimm, MD.)

Upon completion of the distal aortic reconstruction, the pediatric coronary sinus catheter is removed, a crossclamp is applied across the graft, and the innominate artery is reopened with full flow to the body restored. The distal graft then may be cannulated (with a right-angle SoftFlow cannula, a curved metal-tip aortic cannula placed via stab incision, or the accessory limb of a prefabricated branch graft) to assist in CPB and rewarming for the remainder of the procedure. At this point, attention is redirected to completion of the aortic root replacement, performance of a graft-to-graft anastomosis (running 4-0 polypropylene suture), and completion of coronary reimplantation.

## OUTCOMES/PROGNOSIS

### Results of Operation

#### ASCENDING AORTIC ANEURYSMS

Replacement of the ascending aorta has been demonstrated to be a safe and effective procedure for the treatment of chronic aneurysmal disease of the ascending aorta, with operative mortality rates of 2 to 5 percent in the most successful series.[160–162] The operative mortality varies with the acuity of the operation, patient age, left ventricular function, and the extent of operation.[23] The late survival rate after operation is approximately 65 percent at 5 years and 55 percent at 7 years.[160,163–165]

***Marfan Syndrome.*** Before 1968, the outlook for patients with MFS who required surgical repair of aneurysms or dissections involving the aortic root was bleak because of the high operative risk, the nearly prohibitive bleeding rates, and the frequent occurrence of serious postoperative complications.[2] With the advent of CVG repair, valve-sparing aortic root replacement, and modern CPB and myocardial protection, survival is excellent when the operations are performed in an experienced thoracic aortic surgical center.

***Composite Valve Graft Repair.*** In a landmark paper by Gott and associates,[166] the safety and efficacy of aortic root replacement surgery with a CVG technique in MFS patients were outlined. The mortality rate for elective root replacement in 455 patients was a remarkably low 1.5 percent, but the rate was much higher (11.7 percent) in those requiring emergency surgery for acute or chronic type A dissections, emphasizing the importance of early, elective root replacement before ascending dissection. Long-term survival after prophylactic aortic root replacement is also quite favorable, probably because the CVG configuration provides no nidus for clot formation, minimizing the risk of late cerebrovascular accidents. In contrast, MFS patients who have had aortic dissection have a significantly reduced long-term survival, which has been reported at 50 to 70 percent at 10 years.[167,168]

***Valve-Sparing Aortic Surgical Repair.*** Yacoub and subsequently David pioneered what is termed generically as

valve-sparing aortic root replacement. The two surgical approaches are distinct: The Yacoub procedure is referred to as the remodeling technique, and the David procedure is called the reimplantation technique. Both procedures are options for almost all patients with aortic root aneurysms if the aortic valve is structurally normal, but the David procedure protects against further annular dilation. If AR is present because of STJ dilation or cusp prolapse, the AR can be corrected by restoring the normal STJ geometry, shortening the cusp free margin, or both. Structurally abnormal cusps are a contraindication for the procedure, as is an aortic annulus greater than 27 to 29 mm, and CVG with a mechanical valve remains the operation of choice for patients who require anticoagulation for other conditions.[2]

Recent outcome reports from both Yacoub's and David's institutions indicate that the operative mortality rate for either procedure is low, but the need to return to the operating room for bleeding was sixfold higher after a Yacoub remodeling than after a David reimplantation (18 vs 3 percent).[169,170] Probably this is secondary to the long-exposed suture lines running up the aortic pillars and down into the individual sinuses. For prophylactic aortic repairs, long-term survival is excellent with either technique.

The main issue facing patients and clinicians who are deciding between a mechanical CVG and a valve-sparing technique is the durability of the preserved aortic valve. Data from the Yacoub group indicated that 22 percent of patients had moderate AR at follow-up (median follow-up of 3 years).[170] The presence of mild AR early after surgery portended a progression to more severe AR over time. The prevalence of late AR was lower in David's series, but 25 percent of patients at 10 years had 3+ to 4+ AR.[170] A trend toward less AR favored the David reimplantation technique over the Yacoub technique. Another clinical endpoint reflecting valve durability is reoperation. In David's series, it is remarkable that no valve-sparing patient required reoperation, but only nine patients remained at risk at 8 years. This result was superior to Yacoub's experience, in which 17 percent of patients required reoperation by 10 years (17 patients at risk at 10 years). The low numbers of patients who could be evaluated at the late term make these figures suspect secondary to large standard errors. Larger studies with longer term follow-up will be necessary to see if it is possible to assess fully the durability of these two procedures. In summary, the valve-sparing aortic root replacement may present patients with MFS with a reasonable alternative to CVG. Survival is excellent with either technique and complications are rare, but the long-term durability of this repair has not been established. Therefore, patients who select a valve-sparing procedure must accept the risk of reoperation in the future.[2]

## AORTIC ARCH OPERATIONS

As various modifications of surgical technique have been introduced, the morbidity and mortality associated with transverse aortic arch replacement have decreased over the past several decades.[17,18,171,172] Despite these recent advances, providing adequate cerebral protection and preventing cerebral embolization during reconstruction of a calcified and atherosclerotic aorta remain a formidable challenge.[173] In 10 major series, the average operative mortality rate for aortic arch replacement was 13 percent (6–23 percent).[163,174–181] For chronic aneurysms, the operative mortality rate was 11 percent (6–22 percent) and was similar for patients with degenerative aneurysms (6–22 percent) and those with chronic dissections (6–19 percent).[24] Long-term survival has been reported to range from 61 to 82 percent at 5 years and from 31 to 69 percent at 10 years.[164,182,183] Factors independently associated with a worse long-term outcome included symptomatic presentation, angina, the extent of proximal replacement, a concurrent unoperated aneurysm, cardiac dysfunction, stroke, and renal dysfunction.[164]

Contemporary series of total aortic arch replacements show increasingly impressive results, with low perioperative mortality rates and a low incidence of permanent neurologic injury (Table 39-4). These improvements are a direct result

**TABLE 39-4: A Comparison of Results with the Current Technique and a Selection of Other Series of Resections of the Aortic Arch**

| Authors | *n* | Era | Extent of Resection | Technique of ASCP | Perioperative Mortality (%) | Stroke Rate (%) | TND Rate (%) |
|---|---|---|---|---|---|---|---|
| Spielvogel et al.[184,a] | 109 | 1999–2004 | All total arch<br>Arch alone 23.9%<br>Arch and Asc 50.5%<br>Arch and root 15.6%<br>Arch and Desc 2.8% | Initial HCA period, then ASCP via branched graft | 4.6 | 4.6 | 5.5 |
| Numata et al.[185,b] | 120 | 1998–2002 | All total arch<br>Arch and Desc 5% | Balloon-tipped catheter + right axillary perfusion | 5.8 | 0.8 | 5.8 |

(*Continued*)

**TABLE 39-4: A Comparison of Results with the Current Technique and a Selection of Other Series of Resections of the Aortic Arch (*Continued*)**

| Authors | *n* | Era | Extent of Resection | Technique of ASCP | Perioperative Mortality (%) | Stroke Rate (%) | TND Rate (%) |
|---|---|---|---|---|---|---|---|
| Sundt et al.[186,b] | 19 | 1997–2001 | All total arch<br>Arch and Desc 26%<br>Arch and root 16% | 63% ASCP via patch graft to vessels, 53% RCP | 11 | 11 | 16 |
| Okita et al.[135,a] | 30 | 1997–1999 | All total arch<br>Arch and Desc 6.6%<br>Arch and root 3.3% | Balloon-tipped catheter right axillary perfusion | 6.6 | 6.6 | 13.3 |
| Di Eusanio et al.[187,b] | 352 | 1995–2002 | All total arch<br>Arch alone 9.1%<br>Arch and Asc 53.1%<br>Arch and Desc 4.5%<br>Total aorta 23.3% | Balloon-tipped catheters | 6.8 | 3.5 | 5.4 |
| Kazui et al.[188,b] | 220 | 1990–1999 | All total arch<br>Arch alone 1%<br>Arch and Asc 44%<br>Arch and Desc 3%<br>Asc, Desc, arch 51% | Balloon-tipped catheters | 12.7 | 3.3 | 6.0 |
| Wozniak et al.[189,b] | 21 | 1990–1995 | Hemiarch 28.6% only (unilateral)<br>Total arch 71.4%<br>Concomitant root 100% | Right axillary perfusion | 19 | 9.5 | 4.8 |
| Kazui et al.[190,b] | 330 | 1986–2001 | Hemiarch 6%<br>Total arch 94%<br>Asc, Desc, arch 49% | Balloon-tipped catheters | 11.2 | 2.4 | 4.2 |
| Bachet et al.[176,b] | 171 | 1984–1998 | All total arch<br>Arch alone 22.2%<br>Arch and Asc 19.2%<br>Asc ± arch 44.4%<br>Arch and Desc 14% | Direct cannulation, proximal clamps | 16.9 | 12.8 | N/A |

Asc, ascending; Desc, descending; HCA, hypothermic circulatory arrest; ASCP, antegrade selective cerebral perfusion; TND, transient neurologic dysfunction.

[a]Indicates that the series contains nonemergent cases only.

[b]Indicates that the series contains elective, urgent, and emergent cases.

Modified from Spielvogel D, Halstead JC, Meier M, et al. Aortic arch replacement using a trifurcated graft: Simple, versatile, and safe. *Ann Thorac Surg* 2005;80(1):90–95.

of increasing experience, improved perioperative care, and superior myocardial and cerebral protection strategies; however, there is no consensus about the best line of attack for these complex operations, especially with regard to cerebral protection.

## SUMMARY

Ascending aorta and aortic arch pathology represents a continuing challenge for cardiovascular surgeons. Progress over the past three decades, including improved surgical instrumentation and advances in perfusion strategies with resultant improvements in myocardial and cerebral protection have augmented the surgical armamentarium significantly, facilitating the management of complex aortic problems. Increasingly, it is possible to relieve symptoms and prevent catastrophic dissection and rupture with appropriately timed prophylactic repairs even as surgeons strive to maintain more physiologic conditions with valve preservation techniques and in-line reconstructions. Significant challenges remain as surgeons attempt to increase their understanding of these degenerative processes and refine surgical procedures to allow more complex repairs while minimizing surgical morbidity.

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## ASCENDING AND ARCH ANEURYSMS OF THE AORTA BOARD REVIEW QUESTIONS (CHAPTER 39)

1. Which of the following is true regarding heritable disorders of the aorta?
   A. MFS is caused by a single mutation on chromosome 15.
   B. There is enhanced expression of metalloproteinases in MS.
   C. Type II EDS is associated with vascular complications.
   D. Mutations in COLA31 cause LDS.
   E. Turner and Noonan syndromes are both autosomal recessive disorders.

2. Which is true regarding histopathology of the aorta in association with bicuspid aortic valve?
   A. Twenty percent of patients with bicuspid valve have a first-degree relative with bicuspid valve.
   B. There is a five-fold incidence of ascending aortic dilation.
   C. The valve cusps and ascending arterial media arise from the same medial crest cells.
   D. Apoptosis occurs in the valve leaflets.
   E. Fibrillin-1 deficiency is not associated with bicuspid valve.

3. Which is true for other forms of aneurysmal disease?
   A. Syphilitic aortitis is due to chronic inflammation of the adventitia.
   B. Takayasu arteritis primarily results in subclavian aneurysms.
   C. Mycotic aneurysms are typically diffuse and fusiform.
   D. The leading cause of death in Behçet disease is aneurysm rupture.
   E. Giant cell arteritis is not associated with thoracic aneurysms.

4. Which is not an indication for surgery?
   A. Symptomatic aneurysm
   B. Ten percent increase in size over 1 year
   C. Ascending aorta diameter of 4 cm in LDS
   D. Progressive aortic insufficiency
   E. Ascending aorta diameter of 4.5 cm and nonheritable connective tissue disorder

5. Which is true for outcomes after surgery for aortic aneurysm?
   A. Operative mortality for ascending aortic replacement is less than 5 percent.
   B. Long-term survival is not affected by dissection in Marfan patients.
   C. The ideal patient for a valve-sparing operation has an aortic annulus exceeding 29 mm.
   D. There is less aortic insufficiency after the Yacoub operation compared to the David operation.
   E. Chronic dissection is associated with higher mortality after arch replacement.

## ANSWERS

1. **Answer: B.** There is enhanced expression of metalloproteinases in Marfan syndrome. There are multiple mutations in chromosome 15 that can cause MFS. Type IV EDS is associated with vascular complications. Mutations in TGFBR1 and TGFBR2 are associated with LDS. Turner syndrome is a sex aneuploidy syndrome, and Noonan syndrome is an autosomal dominant condition.
2. **Answer: C.** The valve cusps and ascending arterial media arise from the same medial crest cells. Nine percent of patients will have a first-degree relative with bicuspid valve. There is a 9- to 18-fold incidence of ascending aortic dilation. Apoptosis occurs in the aortic wall. Fibrillin-1 deficiency has been implicated in matrix disruption and aortic dilation.
3. **Answer: D.** The leading cause of death in Behçet disease is aneurysm rupture. Syphilitic aortitis is due to chronic mesarteritis and periarteritis. Takayasu arteritis primarily causes occlusive disease of the arch vessels. Mycotic aneurysms are usually saccular and focal. Patients with giant cell arteritis are 17 times more likely to develop a thoracic aneurysm.
4. **Answer: E.** An isolated ascending aorta of 4.5 cm in the setting of a nonheritable tissue disorder is not an indication for surgery. All of the remaining choices are indications for surgical intervention.
5. **Answer: A.** Operative mortality for ascending aortic replacement is less than 5 percent. Dissection adversely affects survival in Marfan patients. An enlarged aortic annulus is less suitable for a valve-sparing operation. The Yacoub operation has a higher incidence of late aortic insufficiency. Chronic dissection has lower mortality compared to acute dissection after arch replacement.

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# Thoracoabdominal Aneurysms

*Ying Wei Lum*
*Glenn S. Roseborough*

**KEY CONCEPTS**

- Epidemiology
  - Thoracoabdominal aneurysms (TAAs) develop in patients with atherosclerotic disease, chronic aortic dissection, and connective tissue disorders (e.g., Marfan syndrome, Ehler–Danlos syndrome).
- Pathophysiology
  - Pathologic processes include chronic inflammation, remodeling of extracellular matrix, and depletion of vascular smooth muscle cells. Elastin depletion in the media layer of the aortic wall is a common finding.
- Clinical features
  - Approximately 80 percent of TAAs are atherosclerotic in nature, associated with smoking, hypertension, hypercholesterolemia, and advanced age. Approximately 20 percent of TAAs develop from chronic aortic dissections and occur in patients with connective tissue disorders. The risk of rupture increases rapidly when aneurysmal diameter reaches or exceeds 6 cm. The most common presentation includes abdominal or back pain, although many TAAs are also discovered incidentally.
- Diagnostics
  - TAAs are classified commonly according to the anatomic scheme developed by Crawford (types I through V). Helical computed tomography and magnetic resonance angiography are the diagnostic modalities of choice, largely having supplanted angiography.
- Treatment
  - Medical therapy includes the reduction of risk factors for aneurysmal expansion (e.g., smoking, hypercholesterolemia) and tight blood pressure control predicated on the use of β-blockers.
  - Interventional therapy includes open surgical, hybrid and totally endovascular repair. Spinal cord protection is of particular concern in all methods of repair.
- Outcomes
  - In-hospital mortality rates after surgery range between 8 and 15 percent in most series. Common postoperative complications include bleeding, respiratory failure, myocardial infarction or cardiac failure, renal failure, and paraplegia. Operative risk increases with advanced age, aneurysm complexity, emergency operation, coronary and cerebrovascular disease, pulmonary disease, and renal failure. Outcomes may be improved with the distal perfusion approach to repair. Five-year survival rates range between 53 and 73 percent.

## INTRODUCTION

Since its introduction by Michael DeBakey in 1956,[1] thoracoabdominal aneurysm (TAA) repair generally presents the most technically challenging and controversial issues in vascular surgery. The surgical repair of TAAs is an undertaking that requires substantial preoperative planning and consideration of a wide array of techniques. Each of these techniques has its champions, and several authors have published comparably good results using widely different methods. In this chapter, the common principles that are applicable to all TAA surgery are described. In addition, most of the surgical techniques currently in use to repair these aneurysms are discussed, with emphasis on those that are preferred at the Johns Hopkins Hospital.

## PATHOPHYSIOLOGY

Insight into the pathophysiology of aortic aneurysm formation at the cellular level has come into focus only recently. The pathologic processes observed in aneurysm development include chronic inflammation, remodeling of the extracellular matrix, and depletion of vascular smooth muscle cells. A basic feature common to all aneurysms is the depletion of elastin, a key structural protein in the media layer of the aortic wall. Normal turnover of matrix proteins is mediated by a family of enzymes called matrix metalloproteinases (MMPs); their activity is regulated by proteins called tissue inhibitors of metalloproteinases (TIMPs). Several MMPs have elastase activity. In separate studies, MMP-2, MMP-3 (stromelysin-1), MMP-9, and MMP-12 [human macrophage elastase (HME)] have been found to have increased activity in aneurysmal tissue.[2,3]

Other components of the inflammatory response appear to play a role in aneurysm formation. The complement fixation pathway seems to be involved in matrix proteolysis, as large amounts of complement-fixing immunoglobulin G (IgG) and complement C3 have been detected in aortic aneurysms.[4] Increased amounts of the inflammatory cytokines tumor necrosis factor-α (TNF-α), TNF-β, prostaglandin $E_2$, and interleukin 6 also have been documented in aneurysm tissue.[5,6] Finally, smooth muscle cells are eliminated at least in part by apoptosis, an active process of cell death associated with increased protein synthesis. This depletes a population of cells that are capable of directing connective tissue repair.[7] All these findings suggest that aortic aneurysm formation is the result of a complex interaction of inflammatory mediators and structural components involved in maintaining the extracellular matrix.

## CLINICAL FEATURES

### Natural History

A majority of TAAs are atherosclerotic in nature and, as with abdominal aortic aneurysms (AAAs), are related to smoking, hypertension, high cholesterol, and advanced age. TAAs are the most common type of aneurysm to develop in patients previously diagnosed with AAAs, occurring in 6 percent of those patients. Approximately 20 percent of TAAs occur in patients who develop chronic aneurysmal dilatation after an aortic dissection and in patients with connective tissue disorders, most notably Marfan syndrome and Ehlers–Danlos syndrome. Compared with AAAs, the natural histories of TAAs have not been well documented owing to the lower incidence of TAAs and the fact that the advanced imaging techniques required to diagnose TAAs have been in general use only for the past two decades. In most patients, slow progressive dilatation ultimately leads to death from rupture if it is not treated (Fig. 40-1).[8–12] The other major cause of death in this population of patients is cardiac disease. The rate of aneurysmal dilatation is approximately a 10-percent increase

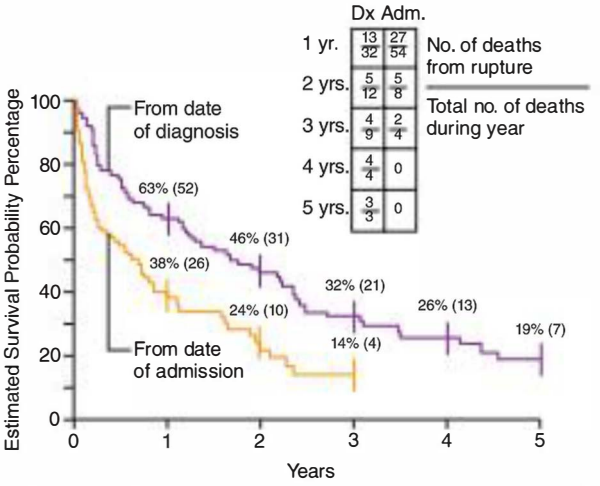



**FIGURE 40-1** Kaplan–Meier probability survival curves from date of diagnosis and date of admission in 94 patients. Numbers of patients at risk at 12, 24, 36, and 48 months are in parentheses. (Reproduced with permission from Crawford ES, DeNatale RW. Thoracoabdominal aortic aneurysm: Observations regarding the natural course of the disease. *J Vasc Surg* 1986;3:578–582. Copyright Elsevier.)

in diameter per year, with higher average rates of growth in patients with TAAs resulting from aortic dissection. The risk of rupture is related to aneurysm size. It is low below 6 cm but increases dramatically with growth in maximum diameter beyond 6 cm; most vascular surgeons recommend conservative therapy for patients with TAAs that are less than 6 cm in diameter and repair if they are more than 6 cm in patients who are acceptable surgical candidates. However, Cambria and coworkers found a higher rate of rupture in patients with TAAs larger than 5 cm.[13] TAAs that result from aortic dissection have been found to be at higher risk for rupture than are atherosclerotic TAAs in separate studies done by Crawford and Denatale and by Pressler and colleagues.[8,14] In addition, Juvonen and colleagues found that patients with TAAs resulting from chronic dissections tended to experience rupture earlier.[15] In that study, the median last known diameter of the aorta in patients who had a rupture was 5.4 cm. Additional risk factors for rupture in that study were chronic obstructive pulmonary disease (COPD) and poorly controlled hypertension. One therefore may consider repair of a TAA that is less than 6 cm in the setting of chronic dissection, particularly in a patient with poorly controlled hypertension and lung disease.

### Classification

TAAs usually are classified according to the anatomic scheme developed by Crawford and coworkers.[16] They are classified as types I through IV. A type I TAA begins in the proximal thoracic aorta and extends to the level of the celiac artery. A type II TAA is the most extensive variety, generally involves the entire thoracic and abdominal aorta, and accounts for a

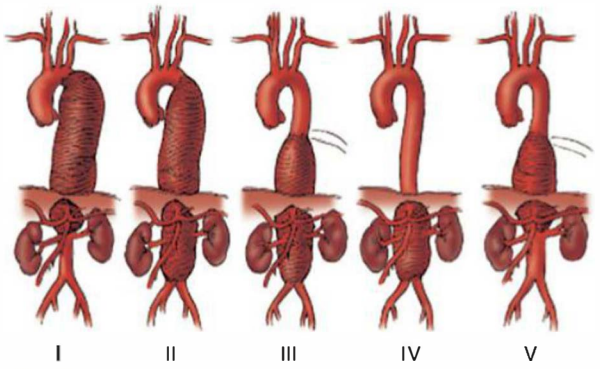



**FIGURE 40-2** Modified Crawford classification of thoracoabdominal aortic aneurysms. *Extent I:* from distal to left subclavian artery to above renal arteries. *Extent II:* from distal to left subclavian artery to aortic bifurcation. *Extent III:* from sixth intercostal space to aortic bifurcation. *Extent IV:* from diaphragm to aortic bifurcation (total abdominal aorta). *Extent V:* from sixth intercostal space to above renal arteries. (Reproduced with permission from Huynh TTT, Miller CC, Estrera AL, et al. Determinants of hospital length of stay a fter thoracoabdominal aortic aneurysm repair. *J Vasc Surg* 2002;35:648–653. Copyright Elsevier.)

large proportion of TAAs that develop years after an extensive aortic dissection. A type III TAA is defined by its proximal extent in the midthoracic aorta, generally is described in the region of the T6 vertebra or the inferior pulmonary vein, and may involve varying amounts of the abdominal aorta. A type IV TAA begins above the celiac axis and extends into the infrarenal aorta. Huynh and colleagues modified the original Crawford classification to include a type V TAA, which begins in the middescending thoracic aorta and terminates at the level of the renal arteries (Fig. 40-2).[17] This classification not only reflects what is encountered at surgery but is important for reporting results, since more extensive aneurysms generally are associated with more complications. Aneurysms that involve only the descending thoracic aorta are not included in this classification and are considered separately, although many of the same principles of TAA repair are used to repair thoracic aneurysms.

## Presentation

Most TAAs are discovered as incidental findings on plain x-ray, computed tomography (CT), or magnetic resonance imaging (MRI) studies obtained for other reasons. Up to 40 percent of patients with TAAs become symptomatic.[18] The symptoms commonly include acute abdominal or back pain. The development of severe acute pain is considered indicative of an impending rupture, and urgent repair generally is recommended within 24 h of presentation. However, the author has observed patients with histories of moderate subacute pain that had been present for weeks to months and resolved with surgical repair; it appears that not all patients with pain are at risk for imminent rupture. Less commonly, TAAs also present with gastric outlet obstruction, renal failure, aortic thrombosis, or failure to thrive. Rupture presents as acute pain with manifestations of shock or sudden death.

## DIAGNOSTIC MODALITIES

Currently, there are no recommended screening tests for TAAs because of their low incidence (1 per 100,000 population[19]) and substantial diagnostic imaging costs. Aortic aneurysms are found on plain x-ray studies about 25 percent of the time. Ultrasound is not useful since the suprarenal aorta is often difficult to image and the thoracic aorta cannot be imaged with this modality. The main diagnostic modalities used for TAAs are CT scanning, MRI, and angiography. A CT or MRI is mandatory for obtaining reliable data on the outer diameter of the aneurysm. A high-quality axial study may provide adequate information for operative planning in straightforward cases; however, helical CT or MRI angiography (MRA) with three-dimensional (3-D) reconstruction is important in defining arch involvement or pathology, especially in visceral branch vessels. Because of the high resolution of these studies, formal angiography rarely is required for preoperative planning (Fig. 40-3).



**FIGURE 40-3** Three-dimensional reconstruction of computed tomography angiogram demonstrating the anatomy of the aortic arch and visceral branches in a patient with a Crawford II t horacoabdominal aneurysm.

In the author's institution, a helical CT scan with 3-D reconstructions is the imaging method of choice. It provides virtually all the information required to plan surgical repair with data that are immediately accessible to the surgeon on a digital workstation. The software for 3-D reconstructions is very user friendly and permits retrieval and manipulation of images with minimal assistance from technicians. In contrast, MRA is slow and expensive and requires extensive postprocessing. It is more prone to false positives for occlusive disease of branch vessels, and reviewing the digital images requires extensive technical assistance. In the author's practice, MRA is reserved for patients with contraindications to CT angiography, such as contrast allergy and renal insufficiency. Aortography played an important role in preoperative planning for TAA repairs in the past, but this modality has been replaced to a large extent by the high-quality imaging of CT and MRA. Nevertheless, the author does use aortography to identify and locate the spinal artery of Adamkiewicz (see below). Recently, however, Japanese investigators have been able to identify this elusive but important structure with CT and MRA.[20,21] The author's institution has not been able to reproduce the Japanese experience reliably thus far.

## MEDICAL THERAPY

Medical therapy consists of controlling risk factors for continued aneurysmal expansion. These patients should be advised to quit smoking, and blood pressure and cholesterol should be controlled strictly. β-Blockers have been advocated to decrease the expansion rate of aortic aneurysms, but a randomized controlled trial conducted in Canada did not confirm their effectiveness.[22] Doxycycline, a known metalloproteinase inhibitor, protects against aneurysm expansion in animal models, and one randomized trial demonstrated decreased expansion rates with daily administration of this drug in a phase 2 trial.[23] However, it is premature to recommend chronic doxycycline therapy to all patients with aortic aneurysms.

## SURGICAL THERAPY

### Preoperative Evaluation and Planning

Because of the high-risk nature of TAA repair, appropriate decision making is imperative in the selection of patients for surgery and in the performance of the surgical procedure to obtain good results (see Fig. 40-4). There are three important components to preoperative evaluation and planning in TAA surgery: determining operative risk, planning the extent and technical sequence of the repair, and selecting surgical adjuncts to minimize morbidity.

The determination that TAA repair is indicated for a patient assumes that the risk of observation is greater than the risk of repair. It is therefore necessary to have a reasonable understanding of a patient's perioperative risk. Postoperative morbidity and mortality is related largely to the cardiac, pulmonary, and renal systems; hence, a thorough evaluation of those systems is imperative. At a minimum, cardiac function should be evaluated with an echocardiogram. An abnormal electrocardiogram (ECG), a history of coronary artery disease or symptoms of chest pain, congestive heart failure, or poor exercise tolerance should prompt evaluation by a cardiologist and some form of stress testing. Dobutamine echocardiography is considered to be contraindicated in patients with aneurysms because of the possibility of precipitating rupture, and so stress thallium scanning and formal exercise testing are the screening diagnostics of choice. Cardiac catheterization should be performed if reconstruction of the ascending aorta or aortic arch is anticipated. Pulmonary function tests, including spirometry and a room air blood gas, should be obtained, since single-lung ventilation usually is required intraoperatively. Renal function and hepatic function are evaluated with blood chemistries. An individualized decision to operate is based on an integration of the estimated risks of rupture and repair for a specific patient after this information has been acquired.

With TAA repair, it is imperative that the surgeon plan the entire operation in advance and anticipate the extent of and steps in the planned repair. This includes the location of the proximal and distal extent of the repair, the location and sequence of aortic clamping, and plans for reimplanting, bypassing, or reconstructing aortic branch vessels. This is important for several reasons. First, the extent of the repair will determine the level of the thoracotomy and the extent of the incision. It also will determine which adjuncts are required intraoperatively, such as cardiopulmonary bypass equipment and neurophysiologic monitoring. The most important consideration in preoperative planning relates to the pathology of the aortic arch. For TAAs involving the proximal descending thoracic aorta, it is crucial that one appreciate the patient's arch anatomy, since arch involvement may warrant the participation of a cardiac surgeon to conduct the cardiopulmonary bypass and hypothermic circulatory arrest. With extensive arch involvement, it may be necessary to perform the repair in stages. For example, in cases in which the aortic arch and the descending thoracic aorta are diseased, the arch can be replaced first, leaving a graft extension (i.e., 'elephant trunk') in the descending thoracic aorta. The descending thoracic aorta is repaired several months later, at which time the new graft replacing the descending thoracic aorta is sewn to the elephant trunk proximally. This staged approach obviates the perilous prospect of clamping and anastomosing the graft to a diseased aortic arch.

### Spinal Cord Protection

The next important consideration in preoperative planning is the way one plans to prevent spinal cord and other end-organ

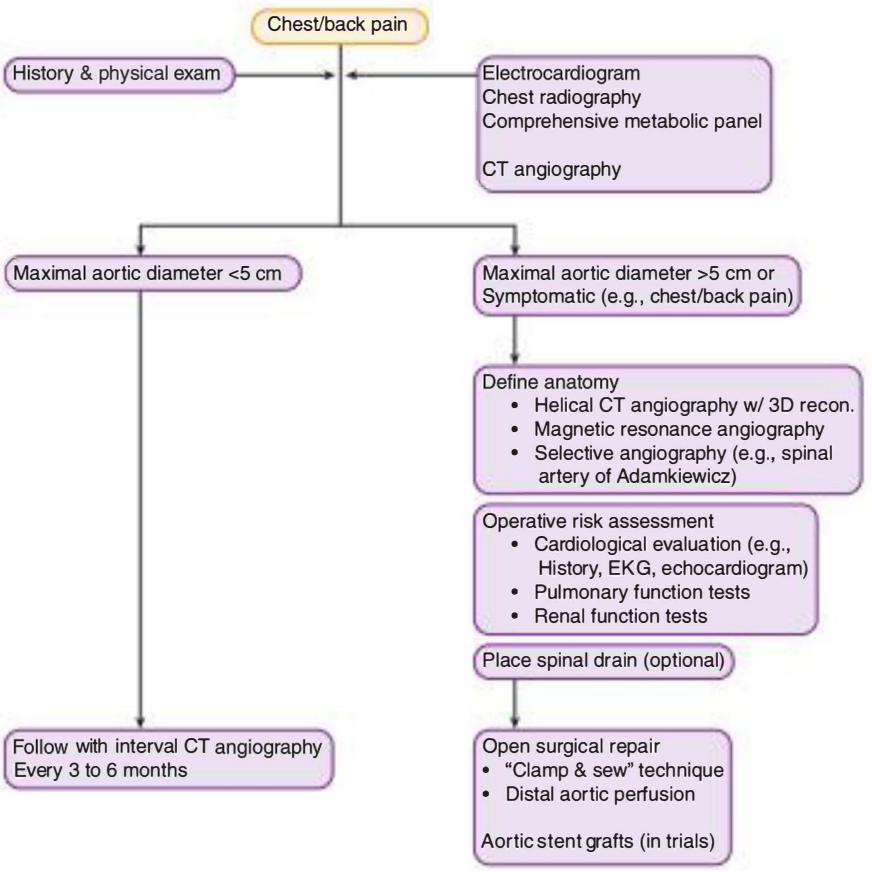



**FIGURE 40-4** Decision-making flowchart.

damage from intraoperative ischemia. Multiple strategies are available to accomplish this goal. With respect to spinal cord protection, they include (1) spinal artery conservation, (2) selective intercostal artery conservation, (3) intraoperative monitoring with somatosensory evoked potentials (SSEP) or motor evoked potentials (MEP), (4) systemic hypothermia, (5) regional hypothermia, (6) lumbar drainage of cerebrospinal fluid (CSF), (7) distal aortic perfusion, either passive or active, (8) aortic conservation with aortic 'tailoring,' and (9) pharmacologic manipulation. With respect to visceral protection, the options include regional or systemic hypothermia and distal aortic perfusion.

## SELECTIVE INTERCOSTAL ARTERY (SPINAL ARTERY) REIMPLANTATION

The most detrimental form of intraoperative ischemia that can occur during TAA repair is spinal cord ischemia, which can occur in up to 40 percent of TAA repairs. The clinical manifestations include a spectrum of spinal cord deficits that can be observed immediately after surgery or up to 3 days later. The most severe form results in complete paraplegia and usually is associated with a mortality rate over 50 percent. The spinal cord becomes ischemic as critical blood flow through intercostal arteries is interrupted when these intercostal arteries are ligated in the course of the aneurysm repair. Over 100 years ago, it was recognized that in humans, a single intercostal artery often gives rise to a branch that provides a major proportion of blood flow to the anterior spinal cord: the spinal artery or the great radicular artery of Adamkiewicz. This artery usually arises from a left-sided intercostal artery between the eighth thoracic (T8) and the first lumbar (L1) vertebrae and has a characteristic radiographic appearance. Animal studies have suggested that preserving the spinal artery can prevent paraplegia.[24] Clinical experience at the Johns Hopkins Hospital and elsewhere has confirmed that preserving the spinal artery in patients undergoing TAA repair can result in improved neurologic outcomes.[25,26] Therefore, at the author's institution, surgeons make an effort to identify the spinal artery of Adamkiewicz preoperatively by performing selective angiography of patent intercostal arteries in the lower descending thoracic aorta (Fig. 40-5). With careful technique, this blood vessel can be identified in up to 86 percent of cases.[27] All efforts are made to conserve the involved intercostal artery at the time of surgery by reimplanting or bypassing to the aortic

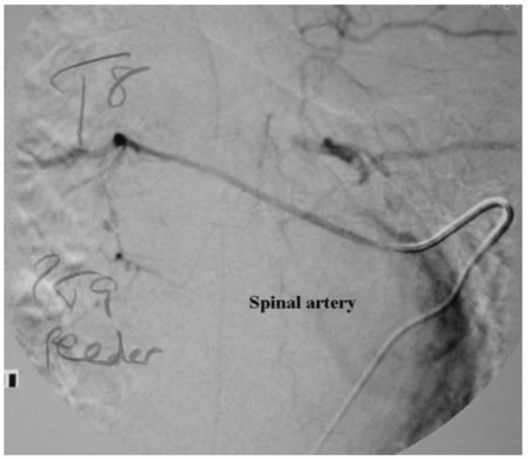



**FIGURE 40-5** Spinal artery angiogram demonstrating characteristic hairpin appearance of spinal artery of Adamkiewicz.

segment from which this intercostal arises or by including this area of aorta within the proximal or distal anastomosis. At the author's institution, it has been found that identifying and preserving the spinal artery is particularly beneficial in repairs of atherosclerotic TAAs, in which the spinal artery is more likely to be one of the few intercostals that are not chronically occluded by aortic thrombus.[28] In this subset of patients, spinal artery identification and preservation resulted in no cases of spinal cord injury in a group of 45 patients. Other authors dispute the value of identifying and preserving the spinal artery.[29,30]

## NONSELECTIVE INTERCOSTAL ARTERY REIMPLANTATION

If the spinal artery is not identified, consideration still is given to reimplantation of intercostal arteries in the lower thoracic region. Safi and colleagues and Cambria and coworkers have shown in separate studies that intercostal artery reimplantation in the T8 to L1 region improves neurologic outcomes,[31,32] and Jacobs and colleagues have reported outstanding results with intercostal artery reimplantation guided partially by MEP.[33,34] The disadvantage of nonselective intercostal artery reimplantation is that multiple intercostals generally must be reimplanted to assure that adequate spinal cord circulation has been maintained in this scenario. Reimplanting multiple intercostals requires a large intercostal patch, which can become aneurysmal in the future, or multiple small patches. The extra suture lines increase the length and complexity of the operation as well as the risk of bleeding. This approach is particularly unappealing to those who employ the clamp-and-sew method of TAA reconstruction, since without distal aortic perfusion, the time that is devoted to reimplanting intercostals adds to the visceral ischemic time because the visceral branch vessels generally are reimplanted after the intercostals.

## INTRAOPERATIVE NEUROLOGIC MONITORING

To help limit intercostal reimplantation, attempts have been made to use intraoperative neurophysiologic monitoring to identify important intercostals and guide selective reimplantation of those vessels. Initial attempts at neurophysiologic monitoring were performed by measuring SSEPs. Laschinger and associates published early work in dogs,[35] showing that SSEP was a sensitive detector of spinal cord ischemia and that distal aortic perfusion could prevent spinal cord ischemia. Subsequent clinical work by that group showed that SSEP loss for more than 30 min predicted spinal cord injury in TAA repair.[36] SSEP is limited in that it detects ischemia primarily in the dorsal spinal cord and can miss ischemic injury in the ventral horns of the spinal cord, where the motor tracts are situated.[37] As a result, intraoperative monitoring of MEPs has been proposed to overcome this limitation,[38] and clinically, MEP monitoring has been shown to be more accurate than SSEP monitoring in detecting spinal cord ischemia.[39,40] Most clinical experience with this technique comes from Holland, where separate groups have had excellent results using MEP to prevent spinal cord ischemia.[33,34,41–43] Using MEP to guide selective intercostal artery reattachment, Jacobs and colleagues achieved paraplegia rates of under 3 percent in a series of almost 200 patients.[34] The author's group has been using MEP since 2000 but has had difficulty reproducing those results. This group has noted a delayed appearance of abnormal MEP signals that can occur with isolated ischemia of the thoracic spinal cord.[44]

## SYSTEMIC HYPOTHERMIA

The development of a hypothermic environment around the spinal cord confers at least partial protection from ischemia during TAA repair. In animal experiments, Colon and coworkers demonstrated that systemic hypothermia protected the spinal cord from periods of ischemia up to 45 min.[45] The benefits of hypothermia can be realized at moderate temperatures (32°C) without incurring the risk of cardiac arrhythmias that occurs at lower temperatures, particularly below 30°C. Moderate hypothermia can be achieved passively or actively with a heat exchanger in a cardiopulmonary bypass circuit; the latter technique is preferred since it allows for active rewarming of the patient at the conclusion of the repair. The disadvantages of this approach include a higher propensity for bleeding stemming from the required anticoagulation and coagulopathies associated with cardiopulmonary bypass and variability in the availability of cardiopulmonary bypass support for some vascular surgeons. In the most extreme form of systemic hypothermia, TAA repair can be performed under profound hypothermia (18°C) and circulatory arrest, as advocated by Kouchoukos and coworkers in this country and by others elsewhere.[46–48] Kouchoukos and coworkers reported very low rates of spinal cord injury with this approach.[46] In the author's practice, this strategy is applied selectively to difficult distal aortic arch anatomy, since circulatory arrest is not without significant

morbidity, including neurocognitive dysfunction. Safi and colleagues reported that profound hypothermia and circulatory arrest did not offer significant benefit compared with moderate hypothermia and partial bypass.[49]

## REGIONAL HYPOTHERMIA

It is also possible to develop spinal cord hypothermia without systemic cooling by using a regional infusion of a cold solution via an epidural catheter. This technique has been championed by Cambria and colleagues at the Massachusetts General Hospital, who have been able to achieve excellent results with respect to spinal cord injury without systemic hypothermia or distal aortic bypass.[32,50,51] With this technique, it is necessary to protect the viscera during extensive TAA reconstructions with cold regional perfusion of those organs as well. Despite good published results, the technique has not been adapted widely at other centers.

## CEREBROSPINAL FLUID DRAINAGE

When the proximal thoracic aorta is clamped, the intracranial and CSF pressures rise. Conversely, blood pressure distal to the clamp drops dramatically. Spinal perfusion pressure, which is represented by mean arterial pressure of the spinal cord minus CSF pressure, therefore drops markedly. CSF drainage reduces CSF pressure in the spinal canal and therefore improves spinal perfusion pressure when spinal perfusion is low intraoperatively as well as in the postoperative period, when CSF pressure may rise as a result of the spinal cord edema that accompanies ischemia–reperfusion injury. Blaisdell and Cooley first demonstrated that decreasing spinal fluid pressure (pharmacologically with intravenous urea) can have a beneficial effect on paraplegia rates in dogs.[52] Subsequently, it was found anecdotally to be useful in resolving delayed-onset paraplegia in the early postoperative period.[53] However, a small prospective randomized study performed by Crawford and coworkers found that CSF drainage had no effect on paraplegia rates.[54] Eleven years later at the same institution, Coselli and colleagues found a statistically significant benefit with CSF drainage in a repeat study, lowering neurologic deficits from 13 percent in the control group to 2.6 percent in the treatment group.[55]

## DISTAL AORTIC PERFUSION

Two fundamental surgical approaches are employed in TAA repair: (1) the so-called clamp-and-sew approach and (2) distal aortic perfusion techniques. The clamp-and-sew method originally employed by DeBakey and Crawford has been employed for over 40 years and still is used by some accomplished aortic surgeons, particularly in patients with less extensive aneurysms.[56–59] In this approach, the aorta is clamped sequentially during the construction of the proximal anastomosis, the reimplantation of critical branches, and the construction of the distal anastomosis. Repair can be performed quickly by an experienced surgeon with less blood loss, since intraoperative anticoagulation is not necessary with this method. However, this technique can expose the viscera to perilously long ischemic times if technical difficulties are encountered with the proximal anastomosis or intercostal artery reimplantation, resulting in end-organ ischemia.

The distal aortic perfusion strategy maintains perfusion of the aorta and its branches distal to the area where the clamps are placed while an anastomosis is created. Distal perfusion can be passive or active. Examples of passive distal perfusion include the Gott aortic shunt,[60–62] an axillofemoral bypass that is constructed before the thoracotomy is begun,[63] and an 'octopus' of catheters whose proximal ends are placed in the Dacron tube graft after the proximal anastomosis is completed and whose distal ends are placed in and perfuse the orifices of the renal and mesenteric arteries while the distal thoracic aorta is repaired.[64] Active distal aortic perfusion involves pumping blood through a centripetal pump into the abdominal aorta while the thoracic aorta is clamped. At the Johns Hopkins Hospital, surgeons believe that this technique is the standard of care in TAA repair as it has several important advantages. A heat exchanger attached to the pump circuit permits active cooling of the patient and, more important, active rewarming at the end of the procedure, when hypothermia contributes to coagulopathy. The advantage of being able to rewarm the patient actively to physiologic temperatures cannot be overstated. The flow in the pump circuit can be adjusted to manipulate the blood pressure proximal and distal to the aortic cross-clamp; typical pump flows range between 1.0 and 2.5 L/min. Proximal hypertension and distal hypotension are corrected by increasing pump flow; proximal hypotension and distal hypertension are corrected by decreasing pump flow. An obstruction to inflow or outflow can be detected by high resistance that is noted in the circuit but would go undetected in a passive shunt. The circuit can be converted quickly to a full cardiopulmonary bypass circuit if the patient experiences cardiac arrest or it becomes apparent intraoperatively that circulatory arrest is required to complete a difficult proximal anastomosis near the aortic arch. Numerous centers have demonstrated improved results in TAA surgery with distal aortic perfusion, and it is the preferred adjunct in most centers.[65–69]

The author's group prefers the use of nonselective distal aortic perfusion, in which the abdominal aorta is perfused via the left femoral artery while the thoracic aortic reconstruction is performed. The patient is cooled to 32°C before spinal cord or visceral ischemia occurs. The mesenteric and renal arteries are clamped and not perfused while the segment of abdominal aorta containing those branches is reconstructed. The author's institution finds that mesenteric and renal revascularization can be accomplished within 30 to 60 min and that renal failure and clinically significant visceral ischemia rarely are encountered with this technique. However, other investigators have shown improved results with selective distal perfusion using direct cannulation of the renal and mesenteric arteries while the visceral abdominal aorta is clamped. Jacobs used selective perfusion (with isothermic blood) in 73 patients and had excellent results, with

permanent renal failure occurring in only 1 patient (1.4 percent) and transient dialysis required in 5 (6.8 percent). Koksoy and associates[70] and Hassoun and associates[71] independently undertook clinical trials to determine whether intraoperative cold perfusion of the viscera could minimize ischemic injury and improve postoperative outcomes, particularly with respect to renal function. Their techniques and findings differed, but both studies found some benefit to cold visceral perfusion. In the Koksoy trial, the kidneys were perfused with cold crystalloid containing steroids and mannitol, and the mesenteric vessels were perfused with warm blood from the left heart bypass circuit. In that study, renal failure was decreased in the cold perfusion group.[70] In the Hassoun trial, all the visceral vessels were perfused selectively with blood that had been cooled to 4°C by being passed through a heat exchanger. The investigators in that trial found no difference in the rate of renal failure but did find improved survival in the group that received cold perfusion.[71]

### AORTIC CONSERVATION

Occasionally, one encounters a moderately dilated distal thoracic aorta while replacing a large aneurysm of the more proximal thoracic aorta in which formal aortic replacement may not be warranted but it may be desirable to try to prevent aneurysmal degeneration of this distal segment to avoid additional surgery in the future. Similarly, it is sometimes necessary to operate on a nondilated aortic segment to correct malperfusion from an aortic dissection. In these situations, it is often preferable not to replace the involved aorta to avoid spinal cord and visceral ischemia. This can be accomplished by using an aortic 'tailoring' procedure developed by G. Melville Williams at the Johns Hopkins Hospital. With this approach, a longitudinal aortotomy is made (in the case of an aortic dissection, the intimal flap subsequently is resected), and the aorta is closed with to a diameter of approximately 2 cm to decrease wall tension and prevent further aneurysmal degeneration. This procedure eliminates the need to sacrifice or reimplant any aortic branches and can be performed with very short cross-clamp times. Williams and colleagues first reported this technique in the treatment of patients with chronic dissecting aneurysms[72] and then applied it to the management of acute aortic dissections complicated by malperfusion.[73] Surgeons at the author's institution routinely tailor a segment of aorta that is up to 4 cm in diameter and occasionally tailor even larger segments. Since Williams began performing this procedure, reoperation has not been required on any tailored segments for subsequent aneurysmal degeneration, with the exception of patients with connective tissue disorders; such disorders, including Marfan syndrome and Ehlers–Danlos syndrome, are contraindications to the aortic tailoring approach.

### PHARMACOLOGIC ADJUNCTS

Most surgeons administer intravenous mannitol before any identified periods of renal ischemia. Mannitol is an osmotic diuretic and free radical scavenger that preserves urine flow after renal ischemia. It does not necessarily prevent ischemic renal failure but promotes a nonoliguric state that is easier to manage clinically.[74–80] In addition, mannitol can ameliorate pulmonary injury associated with aortic surgery.[81]

Acher and coworkers use the partial opioid agonist naloxone for neuroprotection during TAA reconstruction, which they perform with the clamp-and-sew technique and routine ligation of all intercostal arteries. They reported excellent results, with paraplegia rates of 3 percent,[56] although their experience has not been duplicated elsewhere.

A host of pharmacologic agents that interfere with the ischemia–reperfusion injury process have been tested for their ability to prevent spinal cord injury, and they are reviewed thoroughly by de Haan.[82] There are no uniform recommendations for the use of any of these agents. At the author's institution, it has been found that diazoxide, a mitochondrial potassium–adenosine triphosphate (ATP) channel opener, protects against ischemic spinal cord injury in a rabbit model.[83] Further work has shown that this effect is achieved through decreased production of reactive oxygen species in the mitochondria (unpublished data). Current research in cardiology and neurology has focused on poly-adenosine diphosphate (ADP) ribose polymerase (PARP), an enzyme that participates in multiple cellular pathways involved in DNA repair, apoptosis, and ischemic preconditioning. This area of investigation shows promise for improvement in outcomes with respect to partial or delayed neurologic deficits that result from a modest ischemic (and subsequent reperfusion) injury to the spinal cord.

## Operative Technique

The author's protocol for surgical TAA repair begins 2 days before surgery with spinal angiography. A spinal drain is placed by the anesthesiologists the day before surgery so that if a bloody tap occurs during drain placement, there is time for the hemorrhage to resolve without postponing or canceling the operation. After anesthetic induction, the patient is intubated with a single-lumen endotracheal tube that then is exchanged for a double-lumen endotracheal tube to permit single-lung ventilation. Proper placement of the tube is confirmed bronchoscopically. A double-lumen endotracheal tube is important not only to collapse the left lung to facilitate exposure of the aorta in the left chest but also to prevent blood and secretions from depositing in the left lung. Bronchial blockers do not provide reliable isolation of the left lung throughout these long operations and are not recommended.

A Swan–Ganz pulmonary artery catheter and additional central venous lines are placed. A radial arterial catheter always should be placed in the right arm, since a catheter in the left radial artery becomes useless if is necessary to clamp the aortic arch between the left carotid artery and the left subclavian artery. A transesophageal echocardiogram probe is placed, and the patient is put in the right lateral decubitus position on a beanbag with the left arm padded on a Kraus

retractor. The spinal drain is connected to a drainage apparatus with a pop-off valve set to 5 to 10 cm $H_2O$. The hips are rotated obliquely to keep the right groin in the surgical field. The left chest is prepped to the axilla superiorly, the spine posteriorly, and the sternum anteriorly. The abdomen is prepped to the right of the midline. Both groins are prepped to provide surgical access to the femoral vessels. A cell-saver and a rapid infuser should be readily available in the operating room.

The incision is determined by the proximal extent of the aneurysm. In situations where the proximal clamp is placed on or just distal to the aortic arch, as in a type I or type II TAA or for chronic dissection arising just beyond the left subclavian artery, a standard posterolateral thoracotomy is done. The chest is entered in the fourth intercostal space to allow satisfactory exposure of the aortic arch. A type III TAA may be approached through a sixth or seventh interspace incision, whereas a type IV TAA may be approached through an eighth or ninth interspace incision. The incision is carried down onto the abdominal wall, across the oblique muscles lateral to the left rectus abdominus muscle. The retroperitoneal plane is entered deep to the transversus abdominus muscle and developed posteriorly to the psoas muscle under the diaphragm. It is easy to enter the peritoneal cavity inadvertently at this point, especially medially by the edge of the rectus abdominus muscle, where the peritoneum is thin and adherent. The costal margin is divided with heavy scissors, connecting the left chest cavity to the retroperitoneum, and the left internal mammary artery is ligated.

A single simple thoracotomy incision rarely provides enough exposure to repair an extensive TAA. The author's preference is to perform a subperiosteal resection of the rib above or below the interspace that is entered, depending on where exposure is needed most. Additional exposure is provided by 'notching' an additional rib adjacent to the excised rib; a 2-cm segment is excised subperiosteally near the costospinal junction. This approach usually provides adequate exposure to repair even the most extensive TAA. Other surgeons recommend performing a double thoracotomy through one or two skin incisions or a stepwise thoracotomy, in which two or more ribs are divided vertically to extend the thoracotomy through more than one interspace.[84] A self-retaining retractor is placed in the wound and is critical to maintaining exposure of the large field in these long cases: The Omni, Thompson, and Buchwalter retractors are examples of such retractors.

After the chest is entered, ventilation of the left lung is arrested to collapse the lung. The aneurysm, left lung, and heart are inspected. There can be extensive adhesions between the lung and the aneurysm. Filmy adhesions are taken down to mobilize the lung off the aneurysm. If the adhesions are dense, lysis of them can cause extensive intrathoracic and intrapulmonary hemorrhage, and it may be necessary to work around the lung and even open the aneurysm without mobilizing the lung off it. The diaphragm is divided to expose the entire thoracoabdominal aorta, joining the left pleural cavity and the retroperitoneum into a single operative field. This can be done in two different ways. A radial incision can be made from the anterior edge of the diaphragm where the costal margin is divided directly down to the aortic hiatus. This incision is simple to close but results in paralysis of the diaphragm lateral to the incision. Alternatively, the diaphragm can be taken down peripherally, leaving a 2-cm cuff along the chest wall all the way to the aortic hiatus. This is the preferred incision at the author's institution because it preserves the function of the diaphragm and has a minimal effect on postoperative respiratory function, facilitating repair of TAAs in patients with even marginal respiratory status.

The patient then is placed on partial (left heart) bypass with a Bio-Medicus centripetal pump circuit. The inflow site for the cardiopulmonary bypass pump circuit can be one of three sites: the proximal descending thoracic aorta, the left atrium, or the left inferior pulmonary vein. Aortic cannulation can be hazardous, especially in a diseased aorta, and can lead to extensive bleeding while the cannula is in place or after it is removed. The author never cannulates the ascending aorta or the aortic arch because of difficulty with exposure and the risk of stroke. Atrial cannulation requires a pericardiotomy and manipulation of the heart. The preferred site at the author's institution is the left inferior pulmonary vein, which can be accessed in an extrapericardial location. It is easy to locate after division of the inferior pulmonary ligament and mobilization of the lower lobe of the left lung, although occasionally it cannot be used because of adhesions in this area. The patient is anticoagulated systemically with 100 to 150 U/kg of intravenous heparin, and an activated clotting time (ACT) is checked. A pledgeted purse-string suture of 2-0 Ticron is placed in the left inferior pulmonary vein, and the vein is opened after the anesthesiologist delivers a Valsalva breath to prevent air embolism. An angled Sarns venous cannula (20F to 24F) is placed into the pulmonary vein through the purse-string suture and connected to the inflow limb of the pump circuit.

Outflow of the cardiopulmonary bypass circuit usually is delivered via the left common femoral artery. An oblique groin incision is made, and the left femoral artery is dissected out by an assistant while the thoracotomy is being performed. The artery can be cannulated directly, but the author prefers to isolate the artery and sew an 8-mm Dacron graft end to side onto it. A straight 22F or 24F aortic cannula is inserted into and secured to this graft. This technique decreases the chance of creating a dissection in the iliofemoral system and permits antegrade perfusion of the left leg as well as retrograde perfusion up the left iliac system, eliminating the ischemia of the left leg that results from direct cannulation. It also allows the perfusionist to keep the pump circuit flowing into the left leg at a rate of at least 500 $cm^3$/min if it is necessary to clamp the left iliac system during the distal aortic reconstruction.

There are four basic steps in surgical TAA repair: construction of the proximal anastomosis, ligation/reimplantation of thoracic intercostal arteries, reimplantation or bypass of the renal and mesenteric arteries, and construction of the distal anastomosis. One must determine preoperatively if the aortic arch is involved; this will necessitate the involvement of a cardiac surgeon to conduct full cardiopulmonary bypass

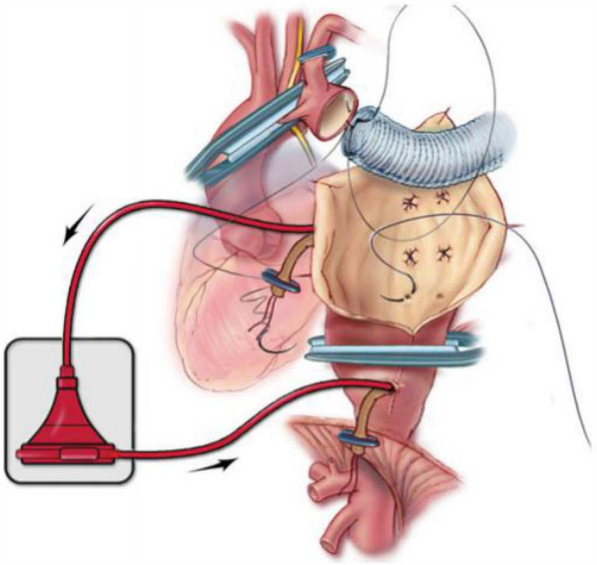


**FIGURE 40-6** Illustration of the construction of the proximal anastomosis during the repair of the descending thoracic aorta just beyond the left subclavian artery. Left heart bypass can be used to provide distal aortic perfusion during the repair. The venous cannula can be placed in the left atrial appendage or left inferior pulmonary vein, and the aortic cannula can be placed in the femoral artery or distal aorta. The upper intercostal arteries generally can be oversewn safely down to the level of T8. (Reproduced with permission from Cohn LH, ed. *Cardiac Surgery in the Adult*, 4th ed. New York: McGraw-Hill, Inc.; 2012.)

and circulatory arrest to effect repair. An aneurysm or dissection that begins just beyond the left subclavian artery may be repaired with a proximal cross-clamp on the aortic arch between the left common carotid artery and the left subclavian artery (Fig. 40-6). This is generally safe but does entail a risk of stroke and recurrent laryngeal nerve injury.

The distal cross-clamp is placed just beyond the level of anticipated aortic transection to minimize distal ischemia during the construction of the proximal anastomosis. The anastomosis between an appropriately sized Dacron tube graft and the proximal aorta is constructed in an end-to-end fashion with running 3-0 polypropylene (e.g., Prolene) sutures. The author prefers to reinforce the anastomosis with strips of Teflon felt incorporated circumferentially in the suture line.

Once the proximal anastomosis is completed and tested for hemostasis, the distal thoracic aorta is repaired. The smooth conduct of this portion of the operation is critical to minimize the risk of paraplegia. Upper left-sided intercostal arteries are ligated before the thoracic aorta is opened if they can be reached behind the aorta, but this can be difficult and can lead to bleeding. The author attempts to dissect out lower left-sided thoracic intercostal arteries and clamp them with atraumatic vascular clamps to prevent back bleeding and steal from the spinal cord circulation, but this is not always possible. The right-sided intercostal arteries are virtually never accessible external to the aorta. The distal clamp is moved to the level of the diaphragm, and the aorta is opened and inspected for patent intercostals branches. The upper intercostal arteries generally can be oversewn safely down to the level of T8 (Fig. 40-6). If the location of the spinal artery is known, the intercostal artery supplying that vessel is reimplanted into the Dacron tube graft with a side-to-side anastomosis or by means of a short interposition graft placed between the Dacron tube graft and a patch of tissue around the relevant intercostal artery; the other intercostal arteries are oversewn. If the spinal artery is not found, serious consideration is given to reimplanting any patent intercostal arteries between the T8 and L1 levels. In this situation, surgeons at the author's institution usually try to reimplant at least one or two pairs of intercostal arteries in the distal thoracic aorta, particularly large ones that back bleed poorly (Fig. 40-7). It may

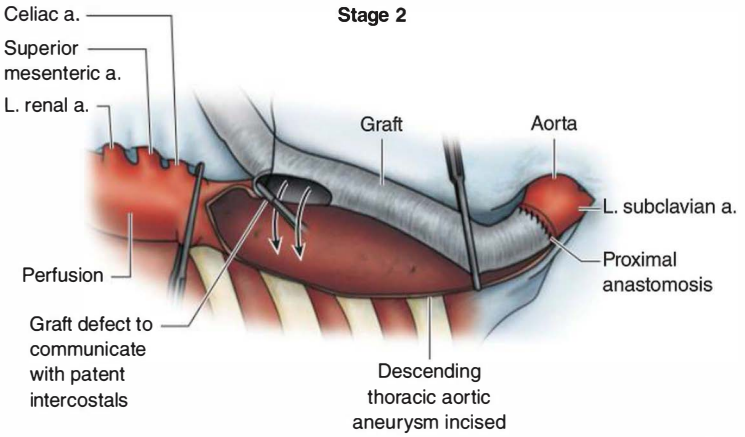



**FIGURE 40-7** Illustration depicting reimplantation of critical intercostal arteries in the side of an aortic graft as a Carrel patch. The abdominal aorta and visceral organs are being perfused during this stage of the procedure by the aortofemoral bypass circuit. (Reproduced with permission from Frank SM, et al. Moderate hypothermia, with partial bypass and segmental sequential repair for thoracoabdominal aortic aneurysm. *J Vasc Surg* 1994;19: 687–698. Copyright Elsevier.)

be necessary to thrombectomize or endarterectomize the aorta to identify patent intercostals. Jacobs employs MEP monitoring to guide selective clamping and reimplantation of intercostal arteries that may be critical to spinal cord perfusion and has reported excellent results, with paraplegia rates of 3 percent.[34] Surgeons at the author's institution have employed MEP since 2000 but have found it to be much less accurate in predicting spinal cord injury. Similar efforts using SSEP monitoring have been even less rewarding. This portion of the operation can take an hour or more, resulting in prolonged visceral ischemia if distal aortic perfusion is not employed.

The visceral abdominal aorta is repaired next. The distal clamp is moved to the most proximal location that will permit repair; if the TAA terminates at the celiac artery, the clamp is placed above the renal arteries so that the kidneys are perfused continuously by the left atrial–femoral bypass circuit. Usually, the clamp is placed below the renal arteries, resulting in visceral and renal ischemia. The celiac and superior mesenteric arteries are dissected out and clamped or controlled from within the aorta with Fogarty balloon catheters once the aorta has been opened. The renal arteries do not back bleed significantly and thus do not need to be controlled. If the TAA terminates near those branches, they can be incorporated into the distal anastomosis. If it extends into the infrarenal aorta, they are reimplanted into the side of the graft (Fig. 40-8). The configuration of the reimplantation depends on the amount of dilatation in this region. With less extensive aneurysms, the celiac, superior mesenteric, and renal arteries can be reimplanted into the side of the graft as a single patch. More often, the celiac, superior mesenteric, and right renal arteries are implanted as one patch and the left renal artery is implanted as a second patch. With extensive aneurysms in this region, the mesenteric vessels are implanted as a single patch and the two renal arteries are implanted as separate patches. The left kidney usually is implanted last and therefore is subjected to the longest ischemic times.

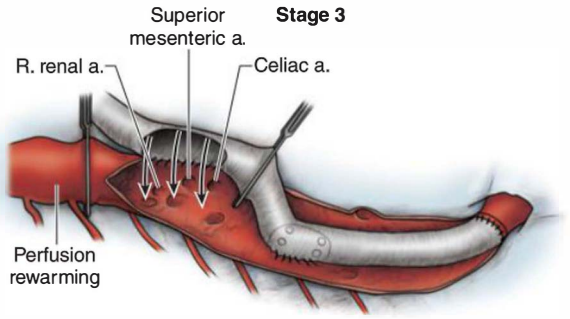



**FIGURE 40-8** Illustration depicting reimplantation of the mesenteric and renal arteries in the side of an aortic graft. Occasionally this can be accomplished as a single patch, but two, three, or even four inclusion patches may be necessary to reimplant the vessels. (Reproduced with permission from Frank SM, et al. Moderate hypothermia, with partial bypass and segmental sequential repair for thoracoabdominal aortic aneurysm. *J Vasc Surg* 1994;19:687–698. Copyright Elsevier.)

Reimplantation of the visceral vessels usually can be accomplished within 30 to 60 min. In these cases, bowel infarction and permanent renal failure are very rare, and so surgeons at the author's institution do not selectively perfuse or shunt the visceral vessels routinely during the visceral vessel reconstruction. Ischemic times increase with the number of patches and can exceed an hour with a difficult reconstruction. If prolonged visceral ischemia is anticipated, consideration should be given to perfusion of the viscera by means of selective catheterization of these vessels and perfusion with either cold blood or crystalloid when the visceral aorta first is opened, as this may reduce the incidence of postoperative renal failure and increase survival rates.[70,71,85] If there is aneurysmal involvement of the branch vessels, interposition grafting from the main Dacron tube graft to those vessels may be required. Surgeons at the author's institution have reported ruptures of aneurysms of the visceral patches, and so they now make every effort to limit patch size, especially in Marfan's disease patients.[86]

Once the visceral patch anastomoses have been completed, the graft is de-aired by back bleeding the mesenteric vessels, and the cross-clamp is placed on the graft at a point distal to the patch anastomoses to permit antegrade visceral perfusion. The distal anastomosis then is performed end to end to the infrarenal aorta if the aneurysm terminates there. If there is iliac artery involvement, a bifurcated graft is sewn to the iliacs first; the proximal end then is anastomosed end to end to the distal aspect of the more proximal Dacron graft. Exposure of the right iliac artery can be difficult from thoracoabdominal incisions and may require a retroperitoneal incision in the right lower quadrant to effect the repair. In cases of iliac artery involvement, every effort is made to revascularize the hypogastric arteries, since spinal cord perfusion may be dependent on the hypogastric circulation after intercostal arteries and lumbar arteries are divided.[34]

After the visceral arteries are reimplanted, the patient is warmed actively with the heat exchanger on the cardiopulmonary bypass circuit while the distal anastomosis is being completed. Once the patient reaches 36.5°C, the bypass circuit is clamped and heparinization is reversed with protamine. The cannula in the pulmonary vein is removed while a Valsalva maneuver is performed. The graft on the femoral artery is clamped and divided, leaving a 1-cm stump of graft on the femoral artery, which then is oversewn. The diaphragm is closed with a heavy running suture after the patient is taken out of the flexed position. The thoracoabdominal and groin incisions are closed in standard fashion. Left apical and basal chest tubes are placed in the left chest, and an Axiom sump drain is placed in the retroperitoneum. The patient's double-lumen endotracheal tube is exchanged for a single-lumen tube before the patient is transported to the intensive care unit. The apical tube is removed on postoperative day 1 if there is no pneumothorax, as is the Axiom drain. The basal chest tube is removed when chest drainage is minimal. The spinal drain is removed on postoperative day 3.

## SPECIAL CONSIDERATIONS

### Thoracoabdominal Aneurysms Related to Chronic Aortic Dissection

TAAs related to chronic aortic dissection pose a number of special technical challenges. First, the proximal anastomosis can be very difficult to perform when the dissection originates very close to the left subclavian artery takeoff. Even cross-clamping between the left carotid artery and the left subclavian artery may not permit a satisfactory repair, and circulatory arrest with deep hypothermia may be required. The false lumen must be entered, and it may be necessary to mobilize the back wall of the aorta off the chest wall to ensure that the adventitia of the back wall is included in the anastomosis. Otherwise, one inadvertently may omit the adventitia from the back wall of the anastomosis, resulting in disastrous bleeding. Once this happens, placement of repair stitches in this area is extremely difficult, and it usually becomes necessary to redo the entire anastomosis.

Second, there are more likely to be more patent intercostal arteries in the descending thoracic aorta than is the case with atherosclerotic aneurysms. Even if the false lumen is thrombosed, it rarely involves the entire posterior wall of the thoracic aorta, leaving many patent intercostal branches. Opening the descending thoracic aorta not only results in massive blood loss from intercostal back bleeding but also may create a huge steal syndrome from the spinal circulation, increasing the likelihood of paraplegia. In these cases, therefore, attempts are made to get external control of as many intercostal arteries as possible with atraumatic spring-loaded clamps before the descending thoracic aorta is opened. Once bleeding is controlled and the surgeon has decided how much of the aorta must be replaced, it can be determined whether these vessels should be reimplanted or ligated.

A third complicating factor relates to the distal intimal flap found in chronic aortic dissections. Malperfusion may result distal to the area where the intimal flap is excised unless care is taken in managing the flap at that point. If the aneurysm terminates in the infrarenal aorta or the distal thoracic aorta several centimeters above the celiac artery, the bypass is stopped temporarily, the distal clamp is removed briefly, and a V-shaped wedge is cut in the intimal flap through the open end of the aorta to stabilize the flap and turn it into a flow divider. Surgeons at the author's institution have prevented distal malperfusion with this technique.

In some cases of TAAs stemming from chronic dissection, large aneurysms of the proximal descending thoracic or the infrarenal aorta are repaired, leaving a moderately aneurysmal distal thoracic or visceral aorta. In situations where the maximum diameter of the distal aorta is dilated but less than 4 cm, surgeons at the author's institution perform a longitudinal aortotomy, resect the intimal flap, and close the aorta to a narrower diameter of 2 cm (Fig. 40-9). This 'aortic tailoring' decreases aortic wall tension, reducing the chances of further aneurysmal dilatation. Of note, in the author's experience, this strategy does not appear to be applicable in patients with connective tissue disorders. This simplified technique preserves intercostal arteries in the distal thoracic aortic segment that otherwise would have to be ligated or reimplanted, decreasing the risk of paraplegia. In the visceral segment of the aorta, the longitudinal aortotomy usually can be opened and closed in less than 20 min, a very short ischemic time that the viscera tolerates very well. This technique can be applied to other areas of the aorta but is particularly valuable in the critical areas of the lower thoracic and abdominal aorta. It also may be employed to correct acute branch malperfusion in an acute aortic dissection. In this situation, the aortic intimal flap is resected and any intimal flap that extends into the orifices of branch vessels is tacked down within the orifices.

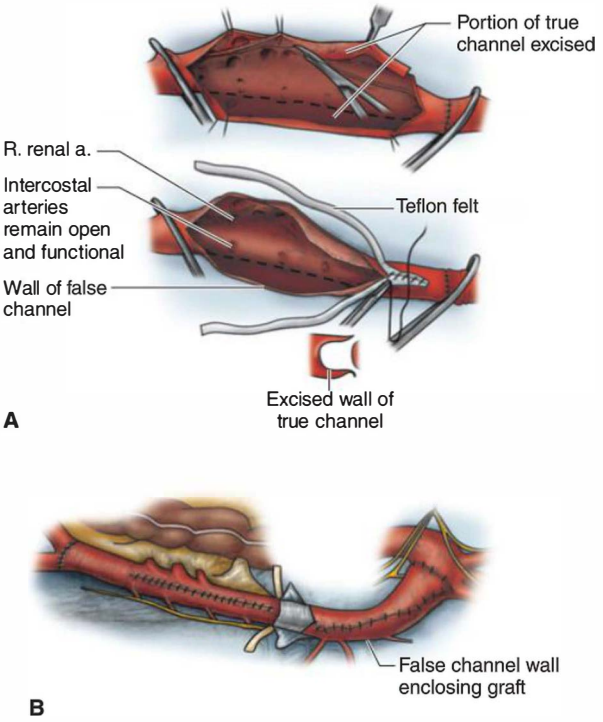



**FIGURE 40-9** Repair of an acute aortic dissection arising in an aneurysm of the descending thoracic aorta complicated by malperfusion of the mesenteric circulation. The aneurysm has been replaced proximally, and the malperfusion has been treated by means of a longitudinal aortotomy, resection of the intimal flap, and closure of the aorta to a small diameter. The suture line is buttressed by strips of Teflon felt. (Diagrams from Williams GM, Schlossberg L. *Atlas of Aortic Surgery.* Baltimore: Williams & Wilkins, 1997. With permission.)

### Ruptured Thoracoabdominal Aneurysms

Ruptured TAAs usually present formidable technical challenges. The patient's symptoms often suggest whether the rupture occurred in the thoracic or the abdominal aorta. If one discovers intraoperatively that a ruptured abdominal

aneurysm is in fact a ruptured TAA, one must first examine the supraceliac aorta at the aortic hiatus. If it is amenable to clamping and the performance of a proximal anastomosis (less than 4 cm in diameter), one should perform a medial visceral rotation to achieve exposure of the suprarenal aorta and control the mesenteric vessels. The infrarenal aorta is controlled distally, and the aorta can be replaced without circulatory bypass. If the supraceliac aorta is too diseased, the laparotomy can be converted to a thoracoabdominal incision across the left costal margin, allowing access to the fifth intercostal space if the costal margin is divided at the level of the xiphoid process. With proximal involvement of the thoracic aorta, consideration should be given to using distal bypass if it is readily available.

More often, the diagnosis of a ruptured TAA is known before exploration. In many such cases, patients have remained stable enough to undergo diagnostic imaging and transfer to a tertiary care center that has the personnel and resources to repair those aneurysms. Selective bias at least partially accounts for the fact that in many published series, the results of repairing ruptured TAAs approach those for repairing ruptured infrarenal AAAs, with survival rates in the range of 40 to 50 percent.[87–93] At the author's center, if surgeons believe the patient is stable enough, they take the additional time to place a spinal drain and neuromonitoring leads if resources are readily available. Needless to say, these judgments are made on an individual basis.

## Endovascular Thoracoabdominal Aneurysm Repair

### HYBRID PROCEDURES

Recent success with treating abdominal and thoracic aneurysms with endovascular technology, and the high complication rates of surgical repair of TAAs, has led to efforts to treat TAAs with endovascular techniques. However, the limited availability of total endovascular repairs with branched/fenestrated stent grafts has resulted in the development of hybrid operations; which combine both open and endovascular techniques (see Table 40-1). This approach consists of first 'debranching' the visceral segment of the aorta with surgical bypasses to the splanchnic and renal arteries distal to their origins. Both renal arteries, the superior mesenteric artery and the celiac are separately and sequentially revascularized with a series of bypass limbs from one or two bifurcated grafts that originate on the distal infrarenal aorta or iliac arteries. The origins of these target vessels are then ligated so that blood cannot flow back into the aorta. Then, the aneurysmal segment is excluded by deploying thoracic stent grafts from the descending thoracic aorta to the infrarenal aorta. There have now been multiple single-institution series comparing hybrid repairs to traditional open repairs for Crawford type I to IV TAAs.[94–98] The majority of these studies had enrolled patients for hybrid repairs if they were deemed unfit or high risk for traditional open surgery. Criteria used to decide if someone was unfit or high risk commonly included advanced age, poor functional status, severe chronic obstructive pulmonary disease, prior open thoracic or TAA repair, and obesity.

There have been two approaches to the timing of hybrid procedures, with some authors recommending a one-stage procedure[94,95,98] and some advocating a two-stage procedure where the visceral bypasses are performed in one operation and the aorta is excluded with stent grafts in a separate, staged procedure (interval between procedures varies from a mean of 3 days to median of 23 days).[96,97,99] Advantages of a single stage procedure include the ability to access the aorta or iliac arteries directly to deliver the thoracic stent grafts (this is an issue particularly in situations when iliac tortuosity or narrowness presents a problem for femoral access), and to ensure accurate deployment of the stent graft relative to the origin of the visceral bypass grafts. Proponents of the two-stage procedure cite several advantages to that technique, including shorter operating times,[99] as well as decreased risk of renal failure given concurrent insults from ischemic time coupled with contrast administration.[96] In addition, delaying the exclusion of the aorta may minimizes the risk of paraplegia

**TABLE 40-1: Table of Recently Published Single-Institution Series Results of Hybrid Procedures for TAAs**

| Author | Year | Institution | No. of Patients | Mortality (30 day) (%) | Paraplegia (%) | Endoleak (%) | Debranching Graft Patency (%) |
|---|---|---|---|---|---|---|---|
| Black[94] | 2006 | St. Mary's, London | 26 (completed) | 23 | 0 | 42 | 98 |
| Chiesa[95] | 2007 | St. Raffaele, Milan | 13 | 23 | 8 | 0 | 100 |
| Zhou[100] | 2006 | Baylor, Houston | 31 (15 visceral, 16 arch) | 3 | 0 | 6 | 95 |
| Brockler[99] | 2008 | Ruprecht-Karls University, Heidelberg | 28 | 14 | 16 | 18 | 89 |
| Patel[96] | 2009 | MGH, Boston | 23 | 17 | 4 | 22 | 90 |
| Patel[97] | 2010 | U of Michigan, Ann Arbor | 29 | 3 | 3 | 34 | 95 |
| Choong[98] | 2010 | St. Mary's, London | 70 | 16 | 10 | — | — |

Reproduced with permission from Patel R, et al. Thoracoabdominal aneurysm repair: hybrid versus open repair. *J Vasc Surg* 2009;50(1):15–22.

known to occur with preoperative hypotension that is more likely to occur when the visceral bypasses are performed.[95]

Regardless of the timing of the approach, spinal drainage is recommended in all patients perioperatively during stent graft deployment. Other technical considerations include the choice of inflow site for retrograde visceral bypass grafting. In general, the site is determined by the distal extent of aneurysmal disease, prior abdominal aortic surgery, and the quality of native aorta and iliac arteries. If the infrarenal aorta has already been replaced, as is frequently the case, the bypass graft can be taken off the existing infrarenal graft in an end-side fashion. Otherwise the visceral grafts are taken off the most proximal normal aorta or iliac artery available, allowing several centimeters of normal aorta above this location to land the distal end of the thoracic stent graft that is used to exclude the aneurysmal aorta.

The drawbacks of hybrid procedures include the concern for endoleaks, which have been reported to be as high as 20 to 40 percent,[94,96,97,99] the unknown durability of retrograde bypass grafting, and the potential for graft enteric erosion. Furthermore, mortality and paraplegia rates for hybrid repairs remain humbling and have not consistently been shown to be better compared with traditional open repair for both high-risk and similar-risk groups.[94, 96] In addition, graft limb thrombosis of the visceral bypasses can result in renal failure or mesenteric ischemia with fatal consequences.

On the other hand, the theoretical benefits of hybrid operations compared to traditional open TAA repair include the avoidance of performing a thoracotomy and single lung ventilation in patients with borderline pulmonary function and avoidance of aortic cross-clamping. Furthermore, there is a significant benefit in terms of reduced visceral ischemic time: The ischemic time to each kidney is reduced to the time is takes to perform a single renal artery anastomosis (usually 5–10 min) and there should be no mesenteric ischemia at all since, when one mesenteric artery is being revascularized, the entire gut and visceral organs should be perfused by the other mesenteric artery via collaterals. This contrasts sharply with the visceral ischemia that occurs during visceral revascularization by the patch inclusion method during open TAA repair, which is typically on the order of 30 to 60 min. Indeed, in the largest series reported to date by Choong et al., hybrid operations have become the preferred repair for type I, II and III TAAs[98] at their institution, since this approach had significantly lower morbidity than open repair.

With a 2-year patient survival rate of less than 30 percent in untreated TAAs,[8] and until total endovascular repair options become more commonly available, such hybrid operations provide a valuable alternative for selected patients, especially some who would otherwise be deemed unfit for surgical repair of their TAAs.

## TOTAL ENDOVASCULAR REPAIR

Numerous case reports and small series have documented successful endovascular repair of aneurysms of the descending thoracic aorta,[101–106] and since obtaining FDA approval in 2005, endovascular repair of descending thoracic aneurysms has become mainstream. Endovascular repair of TAAs has been more limited because of the more complex techniques needed to achieve preservation of visceral flow. However, recent redevelopments in fenestrated and branched grafts have opened the way for a total endovascular approach to treating TAAs (see Table 40-2).

Fenestrated grafts (Fig. 40-10) are designed with nitinol-reinforced holes in the graft fabric that have to be positioned adjacent to the origin of the target visceral artery. Fenestrations, however, have no bearing on the orientation of the target artery (cranially or caudally). Branched grafts (Fig. 40-11), on the other hand, incorporate preattached limbs or cuffs that are attached to the aortic stent graft component.[111] Precise positioning of the fenestration/branch is vital to the success of this procedure and this is ensured by careful preoperative imaging and planning. Once the device is placed at the desired level/orientation of the visceral vessels under fluoroscopy, the fenestration/branch is accessed over a stiff wire into the target vessel, and through this, covered stents are placed.[108,110] This technology can also be applied to aneurysms involving the aortic arch.

Similar to reports of hybrid repairs, the experience with totally endovascular TAA repair consists of single-institution studies where the patients enrolled were deemed

**TABLE 40-2: Table of Recently Published Single-Institution Series Results of Total Endovascular Repair Using Fenestrated and Branched Stent Grafts**

| Author | Year | Institution | No. of Patients | Mortality (30 day) (%) | Paraplegia (%) | Endoleak (%) | Branch Patency |
|---|---|---|---|---|---|---|---|
| Roselli & Greenberg[107] | 2007 | Cleveland Clinic, Ohio | 68/73 successful | 6 | 1.4 (transient paraparesis)<br>1.4 (permanent) | 21 | – |
| Chuter[108] | 2008 | UCSF, California | 22/22 successful | 9 | 14 (transient paraparesis)<br>0 (permanent) | 9 | 99 |
| Verhoeven[109] | 2009 | Nurnberg Hospital, Nurnberg | 28/30 successful | 7 | 13 (transient paraparesis)<br>13 (permanent) | 0 | – |
| Haulon[110] | 2010 | Hospital Cardiologique, Lille | 33/33 successful | 9 | 12 (transient paraparesis)<br>3 (permanent) | 15 | 98 |

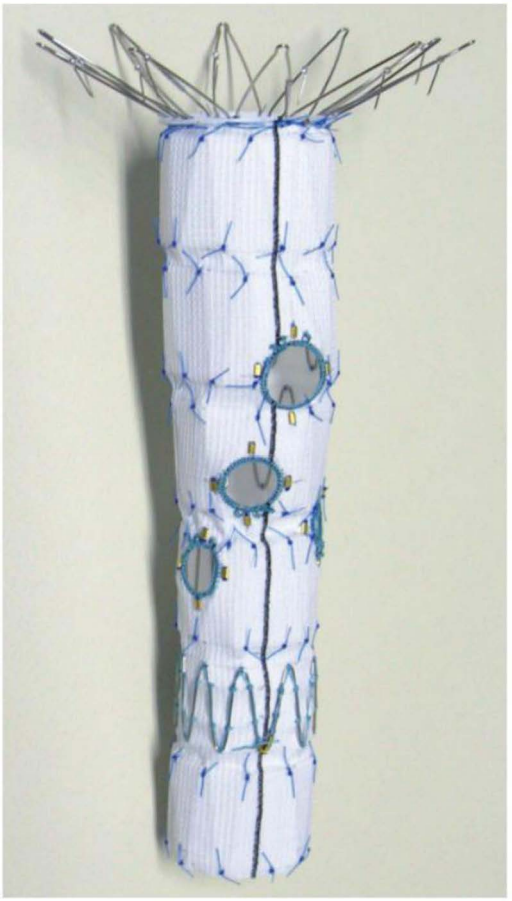


**FIGURE 40-10** Four nitinol-ring-reinforced fenestration, with four attached gold markers each. (Courtesy of Cook Medical, Australia.)

unfit for open surgery. However, unlike hybrid repairs, the early mortality rates after total endovascular repair were significantly lower according to one review.[112] However, this technology is certainly not free of the complications of open repair, including paraplegia, visceral ischemia, and multiorgan dysfunction. The reported paraplegia rates are generally lower, but this may be due to the fact that most reported series contain a higher proportion of Crawford IV TAAs, which inherently are associated with lower rates of spinal cord complications. A major challenge for total endovascular repair is that complex conformational changes occur in the aneurysm after it is depressurized, which can lead to delayed endoleak from component separation, or visceral ischemia from thrombosis of the stent grafts connecting the main aortic graft to the visceral arteries. Nevertheless, the potential advantages of a totally endovascular approach over open or hybrid operations are obvious wherein no body cavities are opened along with the avoidance of aortic cross-clamping and visceral ischemia.[108] The development of this technique is certainly exciting to observe as this technique evolves from surgeon-modified devices[113] to individually custom-designed stent grafts[107–108] and to most recently, progressive reports of standardized, off-the-shelf, multibranched stent grafts.[114]

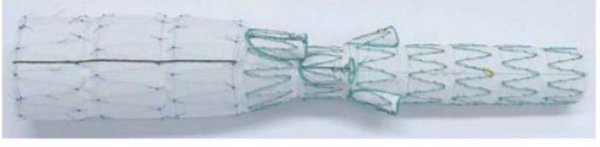


**FIGURE 40-11** Branched thoracoabdominal graft. There are four downward facing side branches for the celiac, SMA, and renal arteries. (Courtesy of Cook Medical, Australia.)

## COMPLICATIONS AND RESULTS

Despite advances in surgical technique and perioperative care, the mortality and morbidity associated with TAA repair remain high. In-hospital mortality rates vary from 8 to 15 percent in most series and may be considerably higher in subsets of patients with extensive aneurysms or comorbidities. Complications occur in up to 75 percent of these patients. Common major complications include reoperation for bleeding, respiratory failure, myocardial infarction or cardiac failure, renal failure, and paraplegia. These postoperative complications, along with preoperative complicating factors such as emergency operation, extensive aneurysms (particularly Crawford type II TAA), advanced age, renal insufficiency, coronary disease, cerebrovascular disease, and pulmonary disease, generally are associated with adverse outcomes.[16–18,32,57,59,115–118] Hospital stays in uncomplicated cases are typically 10 to 14 days and may be considerably longer when there are complications. The pioneering work of Stanley Crawford represents the gold standard for TAA repair with the clamp-and-sew technique. In 1986, Crawford published his experience with TAA repair in 605 patients using this technique.[8] Thirty-day mortality was 8.9 percent; variables predictive of early death were advanced age, prolonged clamp time, COPD, atherosclerotic heart disease, renal failure, and renal artery obstruction. Five-year survival was 60 percent, and a third of late deaths were due to cardiac disease. Renal failure requiring dialysis occurred in 5 percent of patients with normal preoperative renal function and 17 percent of patients with preoperative chronic renal insufficiency. Neurologic deficits in the lower extremities occurred in 11 percent of these patients, with complete paraplegia in 6 percent. The presence of rupture, reattachment of intercostal arteries, the presence of aortic dissection, and the extent of the aneurysm were significant variables associated with neurologic deficits. The last two variables had a particularly strong influence on neurologic outcomes with the clamp-and-sew technique. Neurologic deficits occurred in 30 percent of patients with dissections compared with 7.4 percent of patients without dissections and varied from 2 percent in patients with Crawford IV aneurysms to 28 percent in patients with Crawford II aneurysms (Table 40-3).

## TABLE 40-3: Univariate Relations Between Patient Clinical Variables and Postoperative Early Death, Neurologic Deficit, and Renal Failure

| Variable | No. of Cases | 30-Day Death % | 30-Day Death *P* Value | Neuromuscular Deficit % | Neuromuscular Deficit *P* Value | Dialysis % | Dialysis *P* Value |
|---|---|---|---|---|---|---|---|
| Age (years) | | | | | | | |
| 17–55 | 122 | 2.5 | 0.0323 | 16.4 | 0.0242 | 6.6 | NS |
| 66–65 | 205 | 9.3 | | 12.7 | | 8.3 | |
| 66–70 | 148 | 10.8 | | 10.8 | | 5.4 | |
| 71+ | 130 | 12.3 | | 4.6 | | 10.0 | |
| Sex | | | | | | | |
| Male | 409 | 8.3 | NS | 10.3 | NS | 9.0 | 0.0530 |
| Female | 196 | 10.2 | | 13.3 | | 4.6 | |
| Dissection | 102 | 11.8 | NS | 30.4 | 0.0000 | 9.8 | NS |
| Nondissections | 503 | 8.3 | | 7.4 | | 7.2 | |
| Extent of aneurysm replaced | | | | | | | |
| I | 144 | 9.0 | NS | 10.4 | 0.0000 | 5.6 | 0.0451 |
| II | 159 | 10.7 | | 28.3 | | 6.3 | |
| III | 157 | 10.8 | | 3.2 | | 12.7 | |
| IV | 145 | 4.8 | | 2.1 | | 5.5 | |
| Rupture | 26 | 19.2 | NS | 26.9 | 0.0097 | 15.4 | NS |
| Nonrupture | 579 | 8.5 | | 10.5 | | 7.3 | |
| Symptomatic | 424 | 10.1 | NS | 12.5 | NS | 7.8 | NS |
| Asymptomatic | 181 | 6.1 | | 8.3 | | 7.2 | |
| RAOD | 115 | 15.7 | 0.0049 | 7.0 | NS | 9.6 | NS |
| None | 490 | 7.3 | | 12.2 | | 7.1 | |
| *AHD* | 200 | 12.5 | 0.0302 | 9.0 | NS | 11.0 | 0.0268 |
| None | 405 | 7.2 | | 12.3 | | 5.9 | |
| CVA | 76 | 10.5 | NS | 5.3 | NS | 15.8 | 0.0040 |
| None | 529 | 8.7 | | 12.1 | | 6.4 | |
| COPD | 170 | 14.1 | 0.0051 | 7.6 | NS | 10.6 | NS |
| None | 435 | 6.9 | | 12.6 | | 6.4 | |
| HBP | 434 | 9.9 | NS | 10.4 | NS | 8.3 | NS |
| None | 171 | 6.4 | | 13.5 | | 5.8 | |
| Previous aneurysm repair | 181 | 7.2 | NS | 13.3 | NS | 8.8 | NS |
| None | 424 | 9.7 | | 10.4 | | 7.1 | |
| Renal dysfunction | 84 | 17.9 | 0.0020 | 7.1 | NS | 23.8 | 0.0000 |
| None | 521 | 7.5 | | 11.9 | | 5.0 | |
| Reattached intercostals | 207 | 10.1 | NS | 23.2 | 0.0000 | 6.8 | NS |
| None | 385 | 7.8 | | 4.9 | | 7.3 | |
| Reattached lumbar | 61 | 6.6 | NS | 19.7 | 0.0296 | 9.8 | NS |
| None | 522 | 8.8 | | 10.3 | | 6.7 | |
| Clamp time (min) | | | | | | | |
| 12–30 | 75 | 5.3 | 0.0154 | 2.7 | 0.0000 | 1.3 | NS |
| 31–45 | 203 | 8.9 | | 3.9 | | 7.4 | |
| 46–60 | 177 | 5.1 | | 12.4 | | 7.3 | |
| 61+ | 135 | 14.8 | | 25.9 | | 11.1 | |
| Concurrent aneurysm repair | 51 | 15.7 | NS | 3.9 | NS | 13.7 | NS |
| None | 554 | 8.3 | | 11.9 | | 7.0 | |

NS, not significant ($p > 0.05$) by chi-square test; RAOD, renal artery occlusive disease; AHD, atherosclerotic heart disease; CVA, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; HBP, hypertension.

Adapted from Crawford ES, et al. Thoracoabdominal aortic aneurysms: Preoperative and intraoperative factors determining immediate and long-term results of operations in 605 patients. *J Vasc Surg* 1986;3(3):389–404.

Crawford's experience was updated in 1993, by which time his series included 1509 patients.[18] Once again, rupture, dissection, and the extent of aneurysmal disease were particularly predictive of perioperative death, renal failure, and paraplegia. Other groups using the clamp-and-sew approach have published similar results.[58,59] In the series of Schepen and coworkers, the hospital mortality rate was 11.4 percent, neurologic deficit occurred in 13.8 percent of patients, and renal failure occurred in 14.1 percent.[59] In the series of Mauney and colleagues,[58] hospital mortality was 13 percent, neurologic deficit was 10 percent, and renal failure requiring dialysis was 11 percent. Cambria and associates performed a thorough analysis of their series of 337 patients, in whom the clamp-and-sew technique was used in 93 percent and epidural cooling was used in 57 percent. Variables predictive of death in that series were rupture, emergent operation, intraoperative hypotension, a high transfusion requirement, spinal cord injury, major paraplegia, renal failure, and pulmonary complications.[32] Preoperative variables associated with spinal cord injury were rupture, type I and II TAA, and urgent or emergent operation; intraoperative variables included epidural cooling, sacrifice of T9–L1 intercostals, and intraoperative hypotension as well as prolonged operative time, cross-clamp time, and visceral ischemia. There is evidence that the addition of distal bypass can improve the results obtained with clamp-and-sew techniques, particularly in high-risk patients with extensive aneurysms and aortic dissections. Schepens and colleagues were able to show in their series of 258 patients that left heart bypass reduced mortality, neurologic deficits, and the need for postoperative dialysis.[68] Coselli and coworkers found that left heart bypass was particularly beneficial in patients with type II TAAs, in whom neurologic deficits were reduced from 13 to 5 percent.[69] In a separate publication, Coselli and colleagues reported that the selective use of distal bypass eliminated dissection as a risk factor for postoperative neurologic deficits.[119] Safi and coworkers also demonstrated that left heart bypass in conjunction with CSF drainage could be beneficial in preventing neurologic injury in high-risk patients.[120]

Postoperative renal failure consistently has been shown to be a strong predictor of death in all studies of TAA repair. It typically is associated with a mortality rate of approximately 50 percent. Schepens and coworkers found that age, ischemic heart disease, diabetes, and preoperative creatinine were significant predictors of postoperative renal failure by univariate analysis and were able to develop a stepwise logistic regression equation that accurately predicts the risk of postoperative renal failure by using just two variables: age and preoperative creatinine.[121] Safi and colleagues also examined this subject and found that renal failure was associated with preoperative creatinine, the clamp-and-sew technique, left renal artery reimplantation, and visceral perfusion.[122]

Long-term survival after TAA repair varies between 53 and 73 percent at 5 years. The majority of deaths are due to cardiac disease, although Svensson and associates found that aortic dissection, postoperative neurologic deficit, and renal insufficiency also adversely affected long-term survival.[18] Schepens and coworkers found that early or late reoperation for aortic-related pathology was required in 18 percent (31 of 172) of patients.[123] Cambria and associates found on long-term follow-up that 11 percent of patients (33 of 333) required reintervention after discharge for additional aortic pathology or graft-related problems.[124] Conversely, many patients develop TAAs after having an aneurysm repaired in either the distal or the proximal aorta. Coselli and colleagues examined their results in patients undergoing TAA repair as a second operation after undergoing surgery on the proximal thoracic or distal infrarenal aorta.[125] Surprisingly, they observed a trend toward better results in patients with previous thoracic aortic repair, although that group of patients was younger, had fewer comorbidities, and had fewer emergent repairs than did the group of patients who did not undergo previous thoracic repair. In the patients who underwent TAA repair after distal aortic surgery, the results were quite acceptable, with an in-hospital mortality rate of 12 percent, a paraplegia rate of 4.1 percent, and a renal failure rate of 11.4 percent. Patients also can develop aneurysms of the intercostal or visceral inclusion patches of aorta that are reimplanted onto the Dacron tube grafts. In the author's institution, it was noted that aneurysmal expansion of the inclusion patches occurred in 7.5 percent of patients on long-term follow-up, and therefore, surgeons there recommend implanting small patches of aorta onto the side of the graft, particularly in patients with connective tissue disorders.[86]

Because of the considerable intraoperative technical challenges and the complex postoperative management issues these operations present, they are best performed by experienced surgeons in centers that have extensive critical care resources. Cowan and associates studied the effect of experience (as defined by surgeon and hospital volumes) on outcomes and found that both variables had a significant effect on operative outcomes.[126] Mortality was reduced by more than half when the operations were performed by high-volume surgeons compared with low-volume surgeons; similar reductions in mortality were seen when the procedures were performed in high-volume hospitals compared with low-volume hospitals. Further demonstrating this benefit, Girardi and Coselli showed that even octogenarians can undergo TAA repair with reasonable outcomes when it is performed by an experienced surgeon in a high-volume center.[127] The importance of this volume relationship is further underscored by a recent state-wide database review by Rigberg et al.[128] Even though their report failed to show a volume relationship, they noted that the busiest institution in their database study performed only 14 cases/year and thus their data was unlikely to allow a meaningful assessment of the role of hospital volume in TAA mortality. However, they did note a statewide 30 day mortality of 19 percent, which is worse than the high-volume single-institution reviews that were previously described.

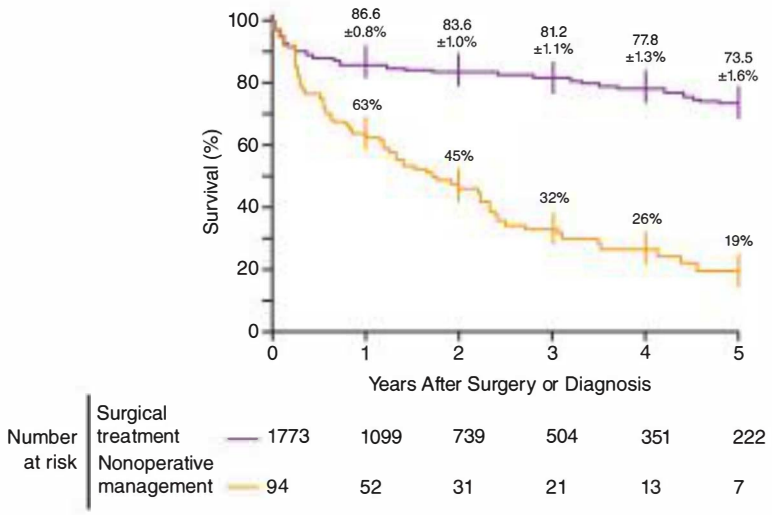



**FIGURE 40-12** Survival curves showing improved survival of a cohort of 1773 patients operated on by Coselli and colleagues compared with t he original cohort of 94 nonoperatively treated patients followed by Crawford. (Reproduced with permission from Coselli JS, Conklin LD, LeMaire SA. Thoracoabdominal aortic aneurysm repair: Review and update of current strategies. *Ann Thorac Surg* 2002;74:S1881–S1884. Copyright Elsevier.)

TAA repair does improve long-term survival, as has been demonstrated by Crawford and Denatale[8] and Coselli and coworkers,[129] but this benefit is dependent on satisfactory surgical results (Fig. 40-12). A good functional outcome is even harder to achieve. Rechtenwald and associates retrospectively studied the functional outcomes of 101 patients undergoing TAA repair over a 6-year period.[130] They found that only 63 percent of patients experienced a good functional outcome at the time of discharge, and that number dropped to 52 percent 1 year after discharge. The results were compromised by a hospital mortality rate of 18 percent and a 12-percent incidence of neurologic deficits; the poor 1-year outcomes were due largely to a 1-year mortality rate of 33 percent. Good functional outcomes correlated with good surgical outcomes; predictors of good outcome were elective operation, short visceral ischemic times, normal preoperative and postoperative renal function, use of left atrial femoral bypass, and absence of postoperative neurologic deficits and pulmonary dysfunction.

## SUMMARY

Repair of TAAs is a challenging exercise that requires considerable preoperative planning, intraoperative skill, and meticulous postoperative care. With a combination of surgical adjuncts, good immediate and long-term results can be achieved. Although there are a number of options for surgical management of these patients, the author's preferred approach includes preoperative CT angiography, selective spinal artery angiography, intraoperative neurophysiologic monitoring, selective spinal artery reimplantation when appropriate, empiric intercostal artery reimplantation when no spinal artery is found, aortic conservation with aortic tailoring in select circumstances, and intraoperative distal aortic perfusion to minimize visceral end-organ ischemia. Postoperative mortality and complications such as cardiac, renal, and respiratory failure as well as spinal cord injury continue to be significant problems. Future advances in the pharmacologic manipulation of ischemia–reperfusion injury as well as the paradigm shift in the development of new endovascular techniques will provide further improvements in the management of these challenging patients.

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## THORACOABDOMINAL ANEURYSMS BOARD REVIEW QUESTIONS (CHAPTER 40)

1. Which is a correct classification of thoracoabdominal aneurysm?
   A. Type I involves the entire thoracoabdominal aorta.
   B. Type II begins at the proximal thoracic aorta and ends at the celiac artery.
   C. Type III begins above the celiac artery and extends into the infrarenal aorta.
   D. Type IV begins in the midthoracic aorta and extends into the abdomen.
   E. Type V begins in the midthoracic aorta and ends at the level of the renal arteries.

2. Which is correct for techniques for intercostal artery reimplantation?
   A. The spinal artery usually arises from a right-sided intercostal artery between T8 and L1.
   B. The spinal artery can be identified in 50 percent of patients using angiography.
   C. Preservation of the spinal artery is not particularly beneficial in repair of an atherosclerotic aneurysm.
   D. A large intercostal patch can become aneurysmal over time.
   E. Nonselective implantation of intercostal arteries between T4 and T7 has been shown to improve neurologic outcomes.

3. Which is true regarding techniques for spinal cord protection?
   A. SSEP detects ischemia in the dorsal spinal cord.
   B. MEP is less accurate than SSEP.
   C. Profound hypothermia and circulatory arrest provides significant benefit compared to moderate hypothermia and partial bypass.
   D. CSF drainage has no effect on paraplegia rates.
   E. Distal aortic perfusion provides no improvement over clamp and sew.

4. Which agent has been shown to be beneficial in multiple trials?
   A. Mannitol
   B. Naloxone
   C. Diazoxide
   D. PARP
   E. Nitroglycerin
5. Which is true regarding outcomes after surgery for thoracoabdominal aneurysm?
   A. In-hospital mortality is 5 to 10 percent.
   B. Complications occur in about 40 percent of patients.
   C. Neurologic deficits occur in about 20 percent of patients.
   D. Five-year survival averages between 50 and 70 percent.
   E. Over 80 percent of patients have a good functional outcome at discharge.

## ANSWERS

1. **Answer: E.** A type V aneurysm, as modified by Huynh and colleagues, begins in the midthoracic aorta and ends at the level of the renal arteries. A type I aneurysm begins at the proximal thoracic aorta and ends at the celiac artery. A type II aneurysm involves the entire thoracoabdominal aorta. A type III aneurysm begins in the midthoracic aorta and extends into the abdomen. A type IV aneurysm begins above the celiac artery and extends into the infrarenal aorta.
2. **Answer: D.** A large intercostal path can become aneurysmal over time. The spinal artery can be identified in over 85 percent of patients using angiography and usually arises from a left-sided intercostal artery between T8 and L1. Both preservation of the spinal artery and nonselective implantation of intercostal arteries in the T8 to L1 region have been shown to improve neurologic outcomes.
3. **Answer: A.** SSEP detects ischemia only in the dorsal spinal cord and is therefore less accurate than MEP. Profound hypothermia and circulatory arrest was not shown to have significant benefit by Safi and colleagues when compared to moderate hypothermia and partial bypass. CSF drainage was shown by Coselli and colleagues to have a significant benefit on paraplegia. Numerous centers have shown improved results with distal aortic perfusion.
4. **Answer: A.** Mannitol is the only agent that has been shown in multiple trials to be effective for both renal and pulmonary protection.
5. **Answer: D.** Five-year survival is about 50 to 70 percent. In-hospital mortality is 8 to 15 percent. Complications occur in up to 75 percent of patients, with only about 10 percent of patients suffering a neurologic deficit. Good functional outcome at discharge is present in approximately 60 percent of patients.

# 41 Aortic Dissection

*Thoralf M. Sundt III*

## KEY CONCEPTS

- Epidemiology
  - Aortic dissection is the most common fatal disease process of the aorta. Increasing awareness of the clinical impact of the condition is reflected by the coining of the term "acute aortic syndrome" (AAS), meant to stand in contrast to the far more common but less lethal "acute coronary syndrome" (ACS). AAS refers to the related processes of acute dissection (AD), intramural hematoma (IMH), and penetrating aortic ulcer (PAU). Although all studies are subject to ascertainment bias as some number of patients surely go undiagnosed, the best estimates of the incidence of aortic dissection derive from a handful of population-based analyses. Estimates from such studies put the incidence somewhere between 2 and 7/100,000. AD is roughly twice as common among men than women, and typically presenting among men in their late 40s to early 60s while women more often present in their 70s. IMH and PAU tend to occur in older patients, and more often affect the descending than the ascending thoracic aorta. AAS occur more frequently in the winter months than summer months, and more often in the morning than evening.
- Pathophysiology
  - AD is a mechanical failure of the aortic wall, and is associated with deterioration of the material properties of that structure. Histologically, this is reflected by medial degeneration—classically referred to as "cystic medial necrosis"—characterized by smooth muscle cell loss and elastin fragmentation. These changes may occur in the setting of some genetic disorders such as Marfan syndrome, Ehlers–Danlos syndrome, and other familial thoracic aortic syndromes, but are also normal consequences of aging. Factors that accelerate this process include hypertension and tobacco abuse, predisposing patients to aortic catastrophe. The inciting event is commonly held to be an intimal tear that permits entry of blood into the weakened media with distal and, in some cases, proximal propagation. In contrast, IMH is thought secondary to primary rupture of intramural vasa vasora. IMH can progress to AD, and some thinkers argue that all AD in fact begin as IMH. PAU may lead to IMH or AD.
- Clinical features
  - Although AD can be painless, most often it is associated with the acute onset of severe, tearing, migratory pain. These symptoms may be associated with unequal extremity blood pressures as well as a changing pulse exam (as the dissection evolves), either hypertension or hypotension, and/or a new murmur of aortic regurgitation. Although the presentation can be dramatic, with associated end-organ complications, such as syncope, cerebrovascular accident, anuria, or ischemic bowel, equally once the acute pain has passed the diagnosis may be subtle. Misdiagnosis of AD as ACS or other conditions such as pulmonary embolus is the rule not the exception. Accordingly, a high index of suspicion and low threshold to perform appropriate imaging studies are critical. The mortality rate associated with AD untreated is estimated at 1 to 2 percent per hour during the first 24 to 48 h and 75 percent at 2 weeks.
- Diagnostics
  - The diagnosis of dissection is critically dependent upon appropriate imaging studies. Electrocardiography (EKG) can be misleading, as compromise of the coronary ostia by the dissection may cause myocardial ischemia. Therefore, neither the presence nor absence of EKG changes rules out dissection. Plain chest radiography may demonstrate a widened mediastinum. Definitive diagnosis, however, is most often made by computed tomography (CT) scanning as it is widely available and is useful ruling out other conditions such as pulmonary embolism. Importantly, however, CT scans may be misinterpreted with AAS due to IMH missed or streak artifacts thought to represent a dissection "flap." The diagnosis can also be rapidly made using echocardiography, either transthoracic or transesophageal, if expert operators are available. Aortography is rarely used today except in the cardiac catheterization laboratory in instances in which the misdiagnosis of ACS was suspected. Magnetic

resonance imaging (MRI) is time-consuming and should only be used in unusual cases in which the diagnosis is evasive.

- Treatment
  - *Medical*: Aggressive anti-impulse pharmacotherapy is the first line of treatment for all AAS. β-Blockade is initiated first with a target heart rate of approximately 60 bpm, with vasodilator therapy (usually with nitroprusside) added to a target SBP of 110 to 120 mm Hg. Patients with type B pathology should continue on medical management unless their pain cannot be controlled or there is evidence of malperfusion or rupture. There is an emerging trend to treat these entities with endovascular stent grafts, although the evidence base for this in the absence of malperfusion is lacking as of this writing. Note that for practical purposes AD, IMH, and PAU are all treated similarly based on anatomic location ("type A" or "type B") and the above-mentioned complications.
  - *Surgical*: Currently, acute "type A" AD, IMH, and PAU are treated in most circumstances surgically. The standard of care is graft replacement of the ascending aorta. Primary treatment with "glues" is unproven and potentially harmful. The extent of distal repair should include the entry site if possible, and in most cases can be confined to hemiarch replacement; total arch replacement is rarely necessary in the acute setting. Most authorities feel the distal anastomosis should be performed "open" under circulatory arrest. Proximally, a regurgitant valve may be resuspended in many instances; however, complete root replacement should be performed if the sinuses are badly dissected or if connective tissue disease is suspected.
- Outcomes
  - The in-hospital mortality rate associated with surgical repair of "type A" dissection is approximately 25 percent, while that for medically treated "type B" dissection is closer to 10 percent. Late outcomes are disappointing, with survival after "type A" dissection at 1, 5, 10, and 15 years being 67, 55, 37, and 24 percent, respectively. Patients with type B dissections fared even less well, with survivals of 56, 48, 29, and 11 percent, respectively.

## BACKGROUND

Acute aortic dissection has been recognized as a clinical entity since the 18th century, with its most famous early victim King George II of England, the notoriously quarrelsome Hanoverian who fought bitterly both with his father and with his son, as well as Spain, France, and most of the rest of Europe during the Seven Years War. The latter conflict spread to the New World in the form of the French and Indian War, draining England's coffers the replenishment of which demanded heavy taxation of the American colonies and stimulated the birth of a nation. Although George II had no known history of high blood pressure, given this disposition, it seems reasonable to assume that hypertension may have played a role in predisposing him to this end on October 25, 1760, while "at stool." Antemortem diagnosis of dissection was first documented a century later by Swaine and Lantham in 1856, and successful surgical repair a century after that in 1955 by DeBakey, Cooley, and Creech.

Advances in surgical therapy have made diagnosis of more clinical relevance, and progress in imaging modalities has made diagnosis practical. Despite this, the majority of patients with acute dissection (AD) are initially misdiagnosed, most often as suffering from an acute coronary syndrome (ACS). Acknowledging this, Villacosta and Roman[1] coined the term "acute aortic syndrome" (AAS), a moniker referring to aortic causes of acute chest pain including AD, intramural hematoma (IMH), and penetrating aortic ulcer (PAU). The three entities are considered by many to lie along a spectrum of disease with similar pathogenesis, clinical features, and treatment algorithms. As AD is far more common—at least in the western world—we will focus on this entity making reference to the latter entities selectively and only as necessary.

## PATHOPHYSIOLOGY

Aortic dissection is associated with longstanding systemic hypertension, tobacco abuse, certain congenital anomalies including bicuspid aortic valve and coarctation of the aorta, as well as defined genetic syndromes including Ehlers–Danlos syndrome and Marfan syndrome. More recently, there is increasing appreciation for other familial thoracic aortic syndromes that may be secondary to mutations in TGF-β signaling or smooth muscle cell actin.[2] All of these result in medial degeneration. Histologically, this is characterized by elastin fragmentation, smooth muscle cell loss, and deposition of ground substance. This appearance was called "cystic medionecrosis" by Erdheim; however, the term has fallen from common usage as it does not accurately describe the pathologic process. Mechanically, the changes associated with medial degeneration result in increased wall stiffness and diminished elasticity.

Primary failure of the aortic wall occurs when the mechanical forces exceed the mechanical properties. It is increasingly apparent that measurement of aortic diameter alone is inadequate as a predictor of risk of dissection with aortic dissection quite clearly occurring at diameters less than 5 cm. Of course, structural failure occurs when wall stress, which is a product of aortic diameter and blood pressure, exceeds wall strength. Unfortunately there is currently

no clinically applicable methodology for assessing the material properties of the aortic wall. In this regard, knowledge of a family history of dissection or presence of a connective tissue disorder such as Marfan syndrome is probably our best clue to the structure of the aortic wall, and likely explains how this catastrophic event may occur even in the absence of significant aortic enlargement.

The century-old hypothesis for the genesis of aortic dissection is intimal disruption followed by propagation of an intimal flap within the media either proximally or distally. The minority view has held that all aortic dissections begin with intramural hemorrhage, which subsequently leads to rupture into the lumen and free communication between the vascular lumen and the propagating tear. Proponents of this view would argue that cases identified as AD have simply missed the IMH phase of the disease process. In support of this hypothesis is the higher frequency distribution of IMH relative to AD in the Far East, where computed tomography (CT) scanning is more frequently performed in evaluating chest pain possibly leading more frequently to capture of the process in its early stages. Although certain proof of the relative contribution of each mechanism to aortic dissection is certainly beyond reach, there is no question that patients with IMH can progress to dissection in at least some instances. The practical implication is that close attention should be paid to IMH and the potential for its malignant progression.

# CLINICAL FEATURES

## Epidemiology

Precise knowledge of the incidence of AD is complicated by incomplete ascertainment due to under diagnosis, which is a particularly vexing problem in this condition. Indeed, in a recent study at a tertiary referral center, over one-third of patients with AAS were misdiagnosed, most often as an ACS, with a clinically significant delay in appropriate treatment and, in most cases, frankly inappropriate treatment with antiplatelet agents (100 percent), anticoagulants (85 percent), or thrombolytics (12 percent).[3] The best possible estimates, however, come from population-based studies such as that reported from western Hungary, which identified AD in 2.9/100,000 inhabitants, with a male-to-female ratio of 1.55:1. Of note, AD was the initial clinical diagnosis in only 15 percent of cases, foreshadowing the findings of Hanson noted above. More recently, Clouse reported from Olmsted county, a small county in southeastern Minnesota principally served by the Mayo Clinic.[4] In this population, the estimated incidence of AD was 3.5/100,000 inhabitants, with 85 percent involving the ascending aorta. The results of a nationwide study in Sweden encompassing over 14,000 cases of thoracic aneurysm and dissection diagnosed between 1987 and 2002 identified an increasing incidence of disease over time, perhaps in part due to better diagnosis, to an incidence of 6.5/100,000 among men and 3.6/100,000 among women.

A great deal of data has been collected by the International Registry of Acute Dissection (IRAD) database. Their studies have confirmed an incidence in men roughly twice that in women, and a difference in age at presentation with women presenting later in life (mean age at presentation 66.7 ± 13.7 for women vs 60.3 ± 13.7 for men), and more frequently presenting late in the disease process with hypotension and tamponade.[5] This same database has demonstrated an increase in the incidence of dissection in the winter months (28.8 percent) versus the summer months (18.9 percent), and in the morning hours (37.4 percent between 06:00 and 12:00 vs 13.9 percent between 00:00 and 06:00).[6]

There are also some important epidemiologic differences between the "variant forms" of AAS, namely IMH and PAU, as compared with AD. In the western hemisphere, IMH is thought to represent approximately 5 percent of AAS.[7] Intriguingly, in the Far East IMH represents up to 50 percent of AAS.[8] Typically, the IMH patient is somewhat older (mean age 68.7 vs 61.7 in the IRAD database) and the disease more typically involves the descending thoracic aorta (60.3 percent vs 35.3 percent in IRAD). Malperfusion is distinctly uncommon as a consequence of IMH. Similarly, the typical PAU patient is also older, and in contrast to the typical AD patient, has extensive atherosclerotic disease.[9] Like IMH, PAU more often involves the descending thoracic aorta, and importantly, the ulcer is often in the mid or distal thoracic aorta.

## Clinical Presentation

Clinically, AD typically presents with sudden-onset, severe chest and/or back discomfort.[10] Characteristically the pain is experienced in the location of the dissection, which is to say those dissections involving the ascending aorta are most often associated with anterior chest pain while those involving the descending thoracic aorta are associated with back pain. The pain may migrate from front to back as the dissection progresses. Dissection can, however, be painless and some data from the IRAD suggest that the mortality rate associated with such dissections may even be higher than that with typical AD.[11] On physical examination, patients may present with either hypertension or hypotension. Differential blood pressure between extremities may be apparent. On occasion, the pulse exam will vary over time as flaps progress and malperfusion appears and disappears. A new murmur of aortic valvular insufficiency is almost diagnostic in association with an episode of severe, sudden pain.

The distinction between acute and chronic dissection is not always clear. The presence of a good history is of course helpful, although patients with chronic dissection may have chest pain of other etiology and, as noted above, AD may not be associated with pain. The presence of pleural or pericardial effusion on diagnostic imaging (see below) suggesting an acute process may be helpful if present. On some occasions, however, one may find oneself operating on an ascending aortic dissection still unsure if it is acute, chronic, or subacute.

## DIAGNOSTICS

Despite interest in the development of biomarkers for dissection, it remains a diagnosis almost entirely dependent upon advanced imaging modalities.[12] Electrocardiography is nonspecific, in so far as dissection may cause coronary insufficiency secondary to compromise of the coronary ostium by the false lumen. In the not-too-distant past, aortography was considered the "gold standard" and many surgeons would not operate without one. Over time, however, other modalities have superseded aortography such that the latter is relevant only when the patient is mistakenly taken to the cardiac catheterization laboratory for presumed ACS, or as part of the therapeutic intervention when placement of an endovascular stent graft is anticipated.

Most often today, a chest CT scan performed in the emergency room will be the first test used to rule out dissection, often one with contrast timed to rule out pulmonary embolism. In most instances, this is sufficient to make the diagnosis of dissection, although one can be fooled by streak artifacts that appear suspicious for a "flap" but are apparent only on one or two images and are associated with a normal diameter ascending aorta. In these instances, it is important to be sure that the apparent intimal flap is present in multiple images. It is also extraordinary to see AD without some degree of enlargement of the aorta itself. Conversely, an IMH or AD with thrombosis of the false lumen may be mistaken for a normal study if the lumen is smooth, regular, and of apparently normal diameter (Fig. 41-1). For this reason, one should look for medial displacement of intimal calcification as a tip-off to dissection or IMH (Fig. 41-2). Properly interpreted, however, the CT scan provides a wealth of information including the anatomy of the dissection at the level of the abdominal aorta and femoral vessels, which may be important if femoral cannulation for cardiopulmonary bypass is chosen (see below). Of course, CT scans can also be easily transported with a patient who is suspected of having dissection such that the surgeons at the receiving hospital may rapidly interpret those studies.

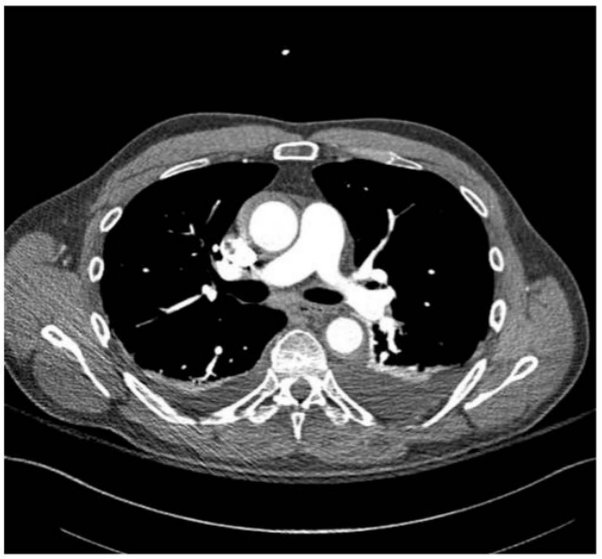


**FIGURE 41-1** Type I IMH with only mild enlargement of the ascending aorta. This can be mistaken for a normal study. Note the left pleural effusion and thickening of the wall of the descending thoracic aorta.



**FIGURE 41-2** Type I dissection with obvious flap in the ascending aorta. Note the medially displaced calcium in the descending thoracic aorta. In the presence of a completely thrombosed false lumen, this may be the only clue that one is seeing dissection versus intraluminal thrombus.

In current practice, a transthoracic or transesophageal echocardiogram is often obtained either as the primary diagnostic modality or as a confirmatory test either in the emergency room, or in our practice, in the operating room. As a primary test, this is perhaps the examination of choice provided skilled interpretation is available, as it imposes no contrast burden on a patient who may subsequently be going to the operating room for a lengthy procedure. Many surgeons are willing to take a patient to the operating room based solely on an echocardiogram demonstrating a mobile septum in the ascending aorta even without a CT scan. Conversely, however, if a CT scan is highly suspicious for type I or II/type A dissection, it is not our practice to insist on a confirmatory echocardiogram in the emergency room. We would rather obtain the transesophageal echocardiogram in the operating room accepting that it may actually rule out dissection than delay the patient's surgical care.

Magnetic resonance imaging (MRI) is employed rarely, and principally as a confirmatory test or as a means of serial follow-up.[12] MRI scanning is time-intensive and not as widely or expeditiously available. The scans themselves are,

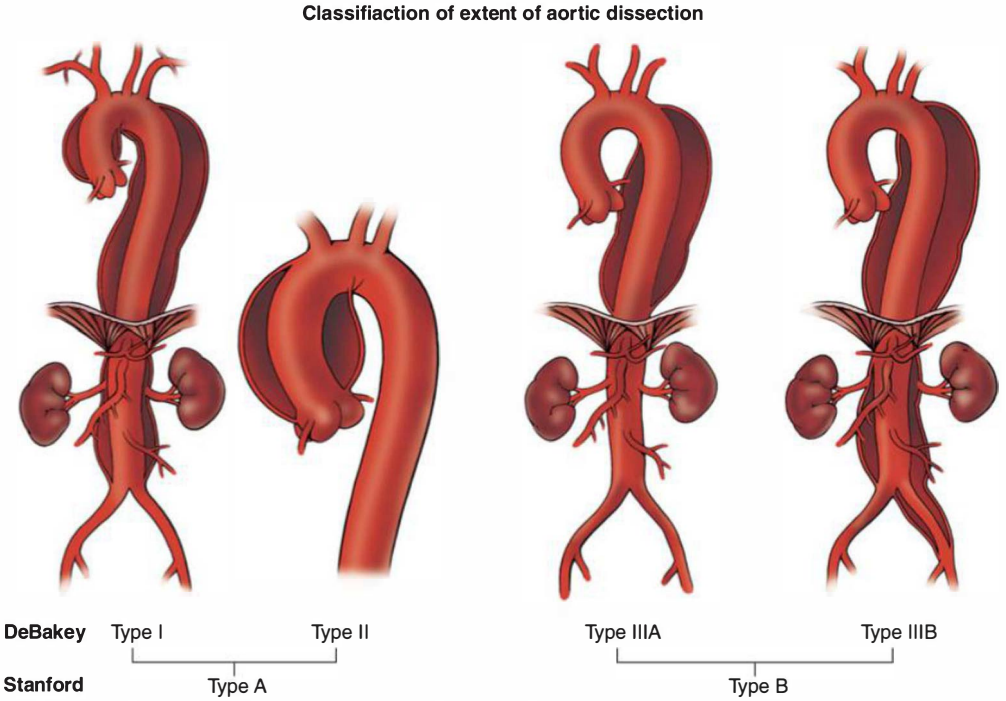



**FIGURE 41-3** DeBakey and Stanford classifications schemes for the extent of dissection.

at least in my opinion, more challenging for the surgeon to interpret as well.

On the basis of the imaging studies described, the AD should be classified according to extent as well as acuity. The two widely accepted classification schemes for acute aortic dissection are the DeBakey classification, which is more detailed but less often utilized because it is more complex, and the Stanford classification, which has been widely adopted particularly by our medical colleagues (Fig. 41-3). Dissections involving the ascending aorta may be DeBakey type 1 extending from the root through the arch into the descending thoracic and thoracoabdominal aorta or DeBakey type II, which are limited to the ascending aorta. The former are the most common, while the latter are the least common. Both are classified by the Stanford scheme as "type A" dissections, a moniker that can be remembered easily as they involve the ascending aorta. Dissections limited to the descending thoracic and thoracoabdominal aorta are classified as DeBakey II or Stanford B. Note that "B" and "III" rhyme, and that type B dissections involve the aorta in the back. It should be noted that a small number of DeBakey type III dissections may propagate somewhat proximally into the arch. Although there is some controversy, they are generally treated as type III dissections. Finally, while again there is some room for argument, dissections may be considered acute if the diagnosis is made within 48 to 72 h, subacute if within 14 days, and chronic if they have been present for over 2 weeks.

In the past, there has been controversy over the need for preoperative coronary angiography. Broadly speaking, however, the current consensus is that obtaining an angiogram is not necessary as concomitant occlusive coronary atherosclerosis is uncommon, and obtaining such studies delays surgical treatment. The potential exception to the rule would be the patient with known coronary disease, for example, status-post coronary artery bypass grafting.

## TREATMENT OPTIONS

The choice of treatment is determined by the location of the disease, the acuity of the presentation, and the presence or absence of complications such as malperfusion (Fig. 41-4).

### Medical Treatment

The first line of therapy for all ADs is anti-impulse therapy. Recognizing that deaths in dissection patients occurred secondary to extension of the dissection and rupture, not the initial tear, Myron Wheat and his colleagues sought to reduce the forces acting to promote these two complications with the aim of delaying surgery until the operation could be performed at lower risk. In a paper presented at the AATS meeting in 1965, they introduced the use of trimethaphan, reserpine, and guanethidine as anti-impulse and antihypertensive agents administered in the acute setting with the

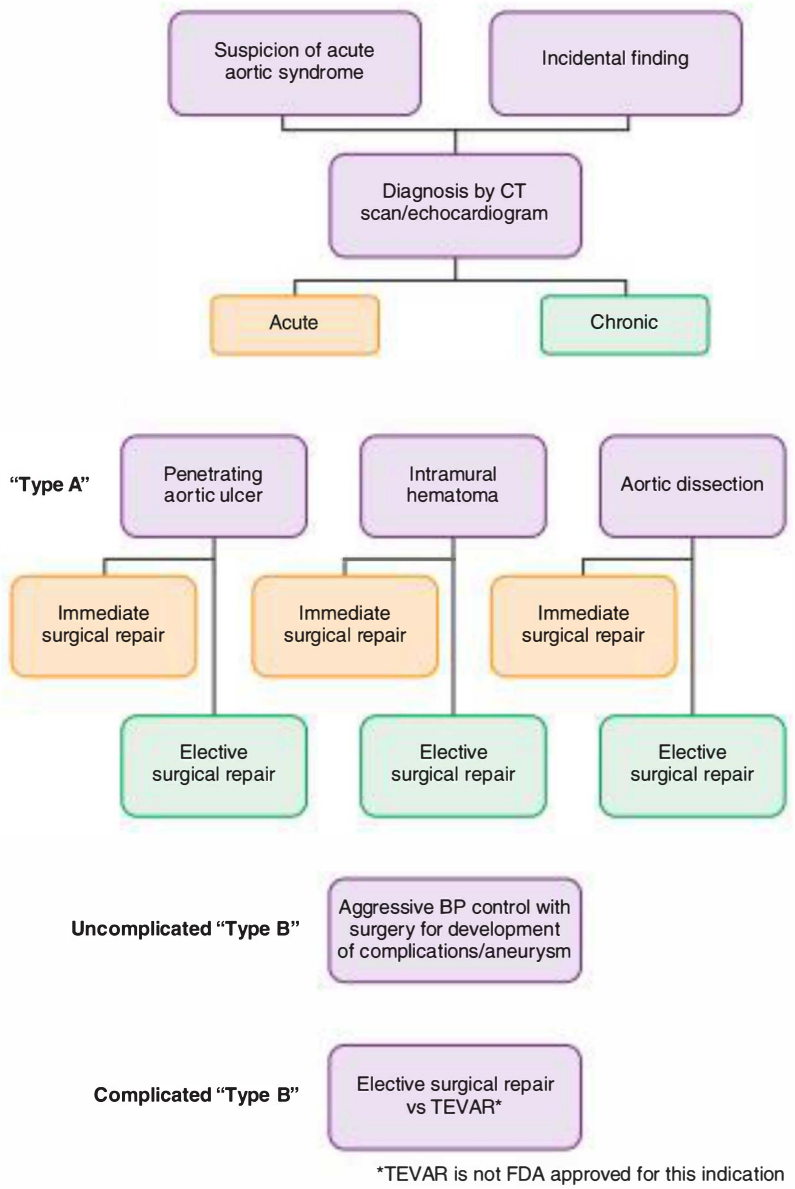



**FIGURE 41-4** Treatment algorithm for aortic dissection and its variant forms.

intention of carrying patients along into a chronic phase in which the risks of surgery would be less. In the current era, short-acting β-blockers such as esmolol are commonly combined with nitroprusside to accomplish these same aims. They should be instituted immediately upon diagnosis of AD, or even before if the clinical suspicion is high.

For uncomplicated acute type III/type B dissections, which is to say those without evidence of malperfusion, continued expansion, and unremitting pain, or rupture, continued medical therapy is preferred to surgical repair. Early studies demonstrated a three-fold higher hospital mortality associated with surgical intervention although it is certain that a greater number of patients with complicated dissections went to the operating room. In the current era, optimal medical management of type III/type B dissections is associated with an in-hospital mortality rate of 8.8 percent overall, and 7.4 percent for those in whom surgical therapy can be avoided.[13] Surgical therapy (endovascular or open) in the University of Texas series was required in 14.5 percent of patients. Overall, for uncomplicated dissections, the mortality rate was 1.2 percent. Initial medical management is, therefore, a well-established therapy for this condition.



FIGURE 41-5 Aneurysmal degeneration of the descending thoracic aorta following repair of type I dissection. Note that the area most prone to enlargement is the proximal portion.

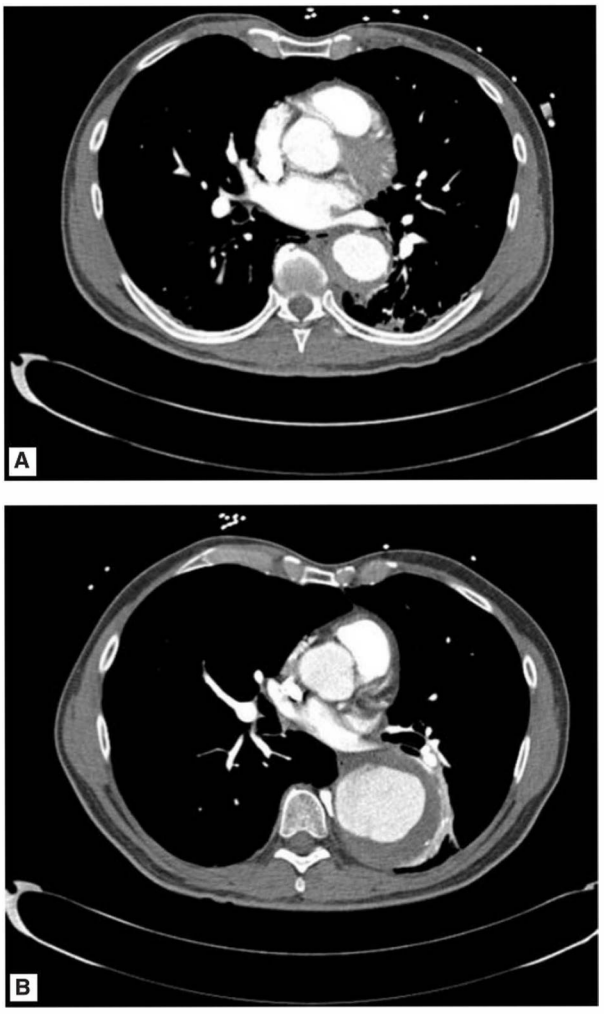



FIGURE 41-6 Aneurysmal degeneration of the descending thoracic aorta 2 years after acute IMH. **A.** Day 0. **B.** Two years.

Endovascular stent grafting as an alternative to medical therapy in type B dissection is increasingly accepted in the setting of complicated disease (see below), but hotly debated in the setting of uncomplicated disease as the outcomes with medical therapy are quite good. Of course, the unanswered question is how many uncomplicated dissections destined to become complicated could be stabilized with an endovascular stent. Long-term imaging surveillance is necessary to determine if aneurysmal dilatation occurs for which delayed surgery would be indicated (Fig. 41-5). This is true for IMH as well as AD (Fig. 41-6).

It should also be noted that ongoing medical therapy (as well as smoking cessation) is critically important in the chronic setting as well. Compulsive blood pressure control no doubt decreases the risk of subsequent dilatation of the dissected descending thoracic aorta. Although it is obviously difficult to demonstrate directly the impact of ongoing hypertension on the risk of reoperation, several studies have demonstrated an inverse relationship between the administration of β-blockers and reoperation. Aortic dissection should, therefore, be considered a chronic disease worthy of ongoing treatment and surveillance. All too many patients are "lost to follow-up" after successful surgical repair of an AD.

For acute type I and II/type A dissections, medical therapy is employed only as a bridge to the operating room. Except in unusual circumstances such as the very elderly or those with significant comorbidities, expeditious surgical therapy is indicated. Special circumstance include the patient with acute stroke or intestinal malperfusion who may be better

served with percutaneous reperfusion and a period of medical stabilization as advocated by Deeb and colleagues.[14] It must be noted, however, that even in the setting of acute stroke, some patients will do well with immediate surgical intervention. A second special circumstance is the patient who presents in a delayed fashion because of either a missed diagnosis or reluctance of the patient to seek medical care. Elefteriades has argued that such individuals can safely be held for semielective treatment after stabilization, full evaluation, and the availability of an elective "daytime" operating room.[15] It would be fair to say, however, that this position is controversial.

## Surgical and Endovascular Therapy

Broadly speaking, immediate surgical intervention is the accepted therapy for AD, IMH, or PAU involving the ascending aorta. The mortality rate associated with nonoperative therapy of dissection of the ascending aorta is 60 to 80 percent, while that for surgically treated patients is between 10 and 20 percent.[16] Of late there has been interest expressed, particularly by investigators in Korea, in managing IMH of the ascending aorta nonoperatively if the aortic diameter is <5 cm and the thickness of the hematoma is <1 cm; however, at the time of this writing, this should not be considered the standard of care.

Acute complicated type B dissections have traditionally been treated by open repair; however, the associated mortality rate may exceed 30 percent. Thoracic endografting is not FDA-approved for dissection; however, some surgeons are employing thoracic stent grafts in the setting of malperfusion as reperfusion can be accomplished quickly.[17] There is also interest in the long-term impact of restoring flow to the true lumen and excluding the false lumen in the upper descending thoracic aorta, which is the region most likely to dilate over time, even in the setting of an uncomplicated dissection. Again, however, this should not be considered the standard of care at this time.

### OPERATIVE PROCEDURES

***Type I and II/Type A Acute Dissections.*** The primary objective in the surgical management of a patient with AD is successful discharge from the hospital alive. This should temper enthusiasm to perform more extensive or elaborate procedures as are sometimes advocated in the literature including total arch replacement with the aim of reducing late reoperation or formal valve-sparing root replacements in the interest of avoiding long-term anticoagulation. This is not to say that, in expert hands, success cannot be achieved in these endeavors. Most ADs treated in the United States, however, are operated on by surgeons who seldom perform such procedures, even in elective circumstances. The primary responsibility of the surgeon facing a patient with an AD is to optimize the chance of the patient walking out of the hospital, and this includes an assessment of one's own comfort and confidence in performing the procedure necessarily to accomplish that goal. From this perspective, facing late reoperation after AD should be considered a good problem.

**Cannulation:** The traditional cannulation for acute aortic dissection is femoral arterial cannulation and venous return via the right atrium. Although alternate sites have been advocated, the femoral arterial approach continues to have vigorous proponents and it certainly must continue to be considered an acceptable approach.[18] Inspection of the preoperative CT scan will allow the surgeon to identify the preferred femoral artery that is perfused by the true lumen. Cannulation of the false lumen runs the risk of creating a malperfusion syndrome that did not exist, however, and for this reason some surgeons advocate bilateral radial arterial monitoring lines. Femoral cannulation also risks atheroembolism secondary to reversal of flow in the descending thoracic aorta, although this is relatively uncommon in the setting of AD as these patients usually have little in the way of atherosclerotic disease. An important exception is patients with penetrating atherosclerotic ulcers as the pathogenesis of their dissection.

An alternative site for arterial inflow that is gaining popularity is the axillary artery.[19] It is a bit more time-consuming to isolate the axillary than the femoral artery, and the axillary artery itself is a soft vessel not without the potential for complications. It too can be dissected, and cannulation of the axillary artery does not always guarantee adequate perfusion of both hemispheres of the brain. Nonetheless, this is certainly the popular trend as it facilitates selective antegrade perfusion (SAP) of head vessels during corporeal circulatory arrest. It is our preference to place a Dacron "chimney" graft on the vessel to minimize the risk of cannulation complications.

Most recently, there have been several groups advocating direct cannulation of the dissected ascending aorta.[20] Although this is a simple and expeditious technique, and should be kept in mind as a back-up, it is one that few surgeons in North America appear to have adopted as a preferred site.

**Perfusion strategy:** In addition to the site of cannulation for cardiopulmonary bypass (CPB), there is ongoing debate over the optimal perfusion strategy. In the early days, dissections were repaired under only mild or moderate hypothermia, with application of a crossclamp below the innominate artery. With the introduction of hypothermic arrest for the repair of degenerative aneurysmal disease, however, the same was applied as an option in the setting of AD. The clear disadvantage of longer pump times and more deranged clotting cascades with resultant bleeding on top of a condition for which perioperative bleeding was already an issue was in part overcome with the development of more hemostatic grafts, as well as systemic medications such as aminocaprioic acid and aprotinin. Indeed, the use of hypothermic circulatory arrest to permit performing an "open distal" anastomosis has become, in the view of many surgeons, the "standard of practice."[21] This approach permits a careful inspection of

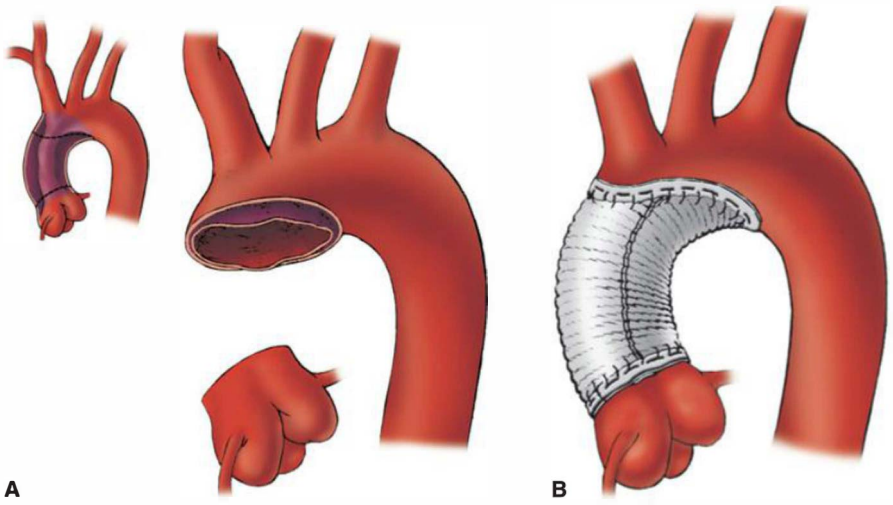



**FIGURE 41-7** Performing the repair under circulatory arrest permits careful inspection of the ascending aorta and arch, as well as latitude to perform an aggressive or conservative hemiarch replacement as per the judgment of the operating surgeon. **A.** At arrest. **B.** The desired end-result.

the anatomy and a more aggressive resection with construction of the distal anastomosis at the level of the pericardial reflection or beyond as a "hemiarch" replacement (Fig. 41-7). Some surgeons insist on resection of the segment of the aorta "with the entry tear" and argue that this can only be accomplished if the arch is inspected. The hope is that such a repair will reduce the risk of late reoperation. Although it is true that complete thrombosis of the distal false lumen appears to be associated with less late dilatation of the false lumen and superior late survival,[22] it is less clear that one can ensure this result by performing the distal anastomosis open. In point of fact, there are very often multiple "tears" in the intima, and the value of "resecting the tear" is unproven despite the reverence with which the "principle" is held. Consistent with this view, if one examines the data objectively, there is no hard evidence that performing an open distal anastomosis improved long-term outcomes.[23] For that matter, aortic dissection is a sufficiently uncommon event that it has been argued that the principles of evidence-based medicine cannot be applied.[24]

Of late, some surgeons have championed a middle-ground, with only moderate systemic hypothermia and SAP.[20] They argue that hemostasis is improved and that cerebral protection is equivalent. As long as one can be certain that corporeal arrest times will be short, this is likely a reasonable approach. If the distal anastomosis proves difficult, however, one might wish one had a bit more of a safety net of hypothermia.

If circulatory arrest is utilized, systemic cooling should be performed for a minimum of 30 min. The target nasopharyngeal temperature should be 18°C at which temperature circulatory arrest for periods of 30 min should be "safe." The arterial perfusate gradient should be maintained at 10° differential during cooling. This provides for even cooling of the brain. Data from the University of Pennsylvania suggest that cooling in excess of 45 min is probably not helpful and therefore in the absence of such monitoring, cooling for this period can be recommended as a safe practice.[25] At the end of the circulatory arrest episode, one should cannulate the graft itself and provide reperfusion in an antegrade fashion. Rewarming should be performed with an arterial-to-venous gradient again no greater than 10°C. Typically, it takes approximately twice as long to warm as to cool. Note that the duration of cooling may be guided by the intraoperative use of electroencephalography. Rewarming is continued in our practice to a temperature of 36°C. We are careful not to overwarm the patient as this can lead to neurologic dysfunction.

Finally, mention of adjunctive cerebral protection strategies is in order. Profound hypothermia was introduced as a simplification of complex branch perfusion strategies. Over time, however, interest grew in adjuncts or even substitutes, in particular retrograde cerebral perfusion (RCP) and, more recently, SAP. RCP was initially embraced by the aortic surgical community, but of late has fallen in use by only a few stalwart groups.[26] More often, SAP is utilized, particularly when the axillary artery is used for arterial inflow, as unilateral SAP requires only control of the origin of the brachiocephalic trunk.

**Extent of repair:** The extent of distal resection should be guided again by the primary aim—which is a live patient at the end of the procedure. Although it is our personal preference to perform a hemiarch replacement under circulatory arrest as we feel that beveling the distal anastomosis adds relatively little to the procedure if one is already committed to circulatory arrest, we have been reluctant to carry the logic further and conduct formal full arch replacement in the setting of AD (Fig. 41-8). This is not,

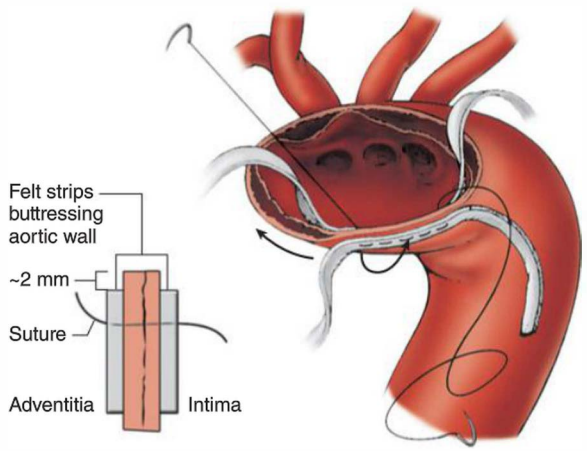



**FIGURE 41-8** Hemiarch replacement is conducted under profound hypothermia and circulatory arrest by first carefully constructing a "felt sandwich." This is a critical step, and if performed correctly assuring that both layers of the aorta are included for the full width of the strips of felt, ensures that both layers of the aorta will be included in the distal anastomosis. Once the reinforcement is complete, the graft-to-sandwich anastomosis can be conducted quickly with focus on including both layers of felt. This is a very hemostatic technique and requires no glues.

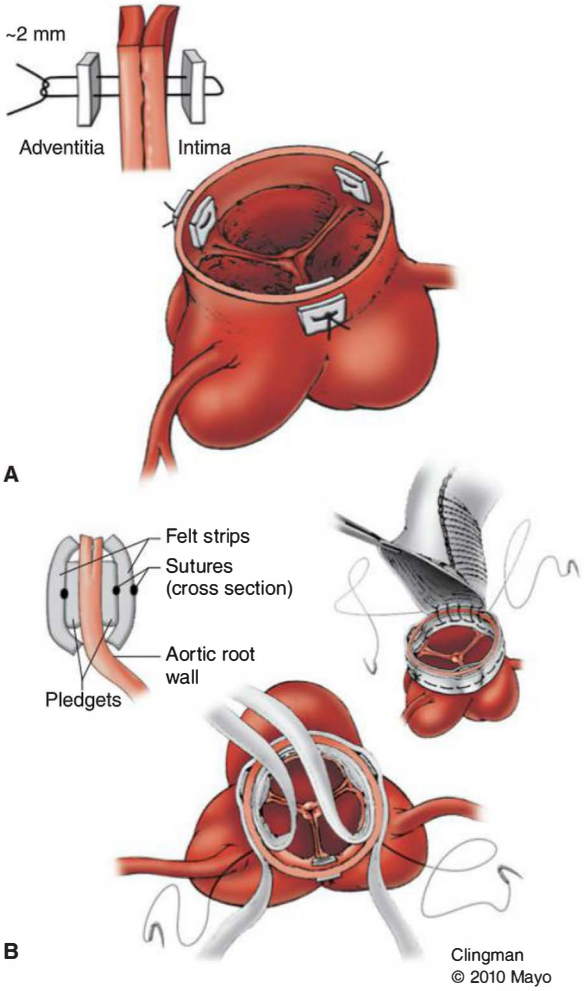



**FIGURE 41-9** The proximal anastomosis can often be performed at the sinotubular junction. **A**. If there is aortic regurgitation secondary to prolapse of a commissure, the commissures can be resuspended with pledgeted mattress sutures. **B**. I then create a proximal aortic sandwich analogous to the one created at the distal anastomosis. Care must be taken not to purse-string this reinforcement. (**B**: By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

however, a universally held position, and total arch replacement is strongly advocated by some, in particular among Japanese groups.[27] The argument is that in their hands total arch replacement adds little or no operative risk, and that is prevents late reoperation. The arch itself, however, does not usually dilate except in Marfan syndrome. Much more commonly, it is the proximal descending thoracic aorta that enlarges. Studies from the United States, however, have suggested that the distal extent of resection has no influence on reoperation.[28] The same logic applies to the current enthusiasm for inserting covered stent grafts distally in association with either arch replacement and a "frozen elephant trunk" or otherwise. Some early studies have suggested a not-inconsiderable incidence of paraplegia with these approaches, a complication that gives one particular pause as a consequence of a prophylactic procedure.

Similarly, the proximal extent of resection has not been shown to impact reoperation.[28] Quite often a valve resuspension can be performed if the dissection has disrupted a commissure causing aortic regurgitation. The commissure can be tacked up and reinforced with the proximal anastomosis (Fig. 41-9). Composite root replacement has been associated in some series with an increased operative risk. This is probably particularly true in practices where root replacement is not commonly performed. On the other hand, a young patient—and certainly a patient suspected of having Marfan syndrome—will probably do better in the long run with a formal root replacement. Patients with bicuspid aortic valves and ADs should likely have formal root replacement as well. The recent introduction of the David valve-sparing operations excites interest in this area as well. Again, our only admonition would be that a more complex procedure, if it adds operative risk, may not be in the best interest of the patient.

Root replacement may be with either a mechanical valve conduit or a biologic prosthesis. There are stentless Xenograft root prostheses available; however, not all hospitals will keep an inventory on hand and not all surgeons may be comfortable with implanting them. A simple alternative is to sew a Dacron graft to the sewing ring of a stented xenograft creating a "homemade" biologic

composite graft. The Dacron graft should be 3 to 5 mm larger than the nominal size of the stented xenograft. I typically run a 4-0 Prolene along the sewing ring of the xenograft through the Dacron graft as an over and over stitch. I then implant the root just as I would a mechanical valve conduit catching both the sewing ring of the valve and the Dacron graft with each valve stitch. The biologic conduit is then seated in place and coronary buttons reimplanted in the usual manner.

An appealing option, at least from a theoretical standpoint, is formal valve-sparing repair (VSRR) using either the David reimplantation technique[29] or the Yacoub remodeling technique.[30] Some surgical groups with extensive experience in VSRR have reported gratifying results; however, again it should be emphasized that survival of the patient is the highest priority. As most dissections in the United States are repaired by surgeons who perform aortic repair uncommonly, this is no condition in which to add the complexity of an aortic reconstruction that the surgeon also performs rarely. A middle ground is replacement of the noncoronary sinus alone as a "modified Yacoub" when the dissection has extended particularly into this sinus as is often the case (Fig. 41-10). This is certainly preferable to the use of glue (see below). When we perform a full root, we currently prefer the David reconstruction (Fig. 41-11).

In some instances, the coronary buttons themselves may be difficult to reimplant. This may be secondary to the fragility of the vessels themselves or scar tissue if the patient has undergone previous root surgery of any type. In these cases, a Cabrol coronary reconstruction can be lifesaving (Fig. 41-12). A 6- or 8-mm Dacron graft may be sewn end-to-end to the coronary buttons and then brought to the ascending graft as shown. If such a reconstruction is performed, one must be particularly attentive to the risk of kinking of the graft, particularly after weaning from bypass. A graft configuration that looks satisfactory prior to a weaning from bypass may not be ideal when the right ventricle is full and the right coronary button is brought higher and closer to the graft itself.

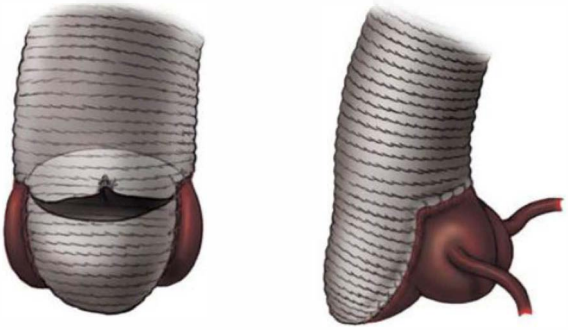


**FIGURE 41-10** If the noncoronary sinus is dissected, it can be replaced with a tongue of Dacron graft.

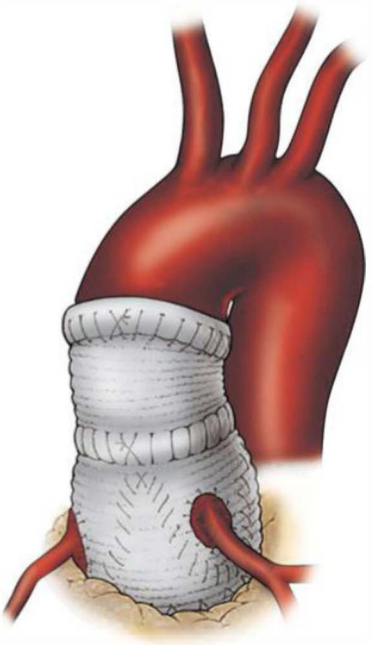


**FIGURE 41-11** When we perform a valve-sparing root reconstruction we currently prefer the David reconstruction. We use two grafts, the sinus portion being 6 mm larger than the tubular graft, with the latter sized to the annulus.

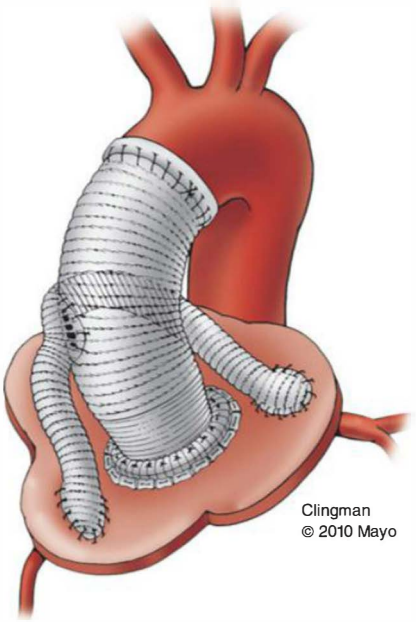



**FIGURE 41-12** If the coronary ostia are difficult to reimplant due to either fragility or scar from prior surgical interventions, they can be reconstructed with a 6-mm Dacron graft carefully anastomosed first to the ostia themselves and then to the main graft in a location that provides a comfortable lie. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

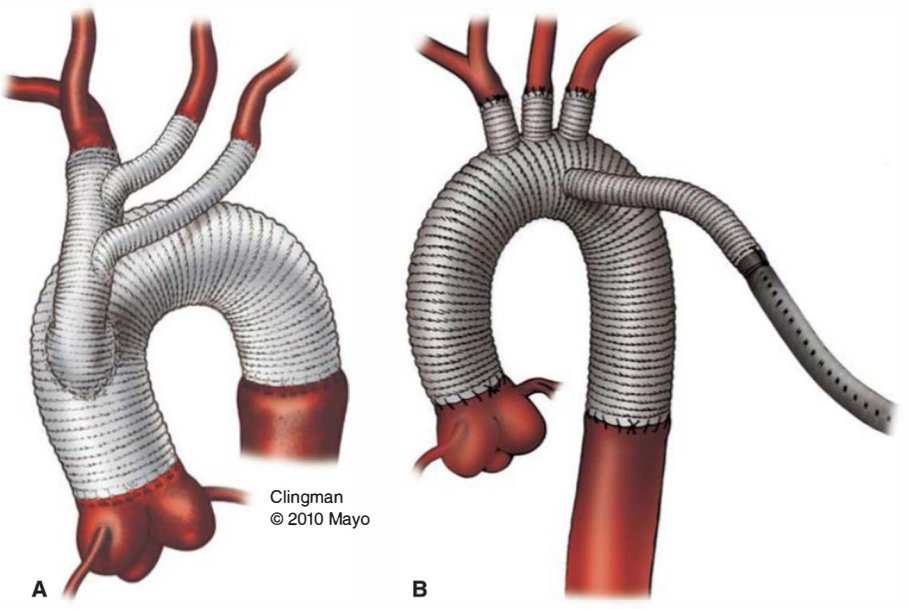



**FIGURE 41-13** If the arch needs to be reconstructed we currently prefer to do so with individual brachiocephalic anastomoses with either a trifurcated branch-graft (**A**) or branched arch graft (**B**). (**A**: By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Although there has recently been great enthusiasm for the use of adhesives in the setting of AD, it is not our practice to use these agents as we have been quite concerned about the potential for tissue necrosis secondary to their chemical make-up. We have seen any number of patients with pseudoaneurysms after repair of dissection who have, at reoperation, enormous quantities of biologic glue and associated obliteration of tissue planes and gray, fragile, fixed tissues.[31] Instead, we have used a time-honored and old-fashioned technique where a Teflon felt sandwich is created at both the proximal and the distal anastomoses. Strips of felt are placed inside and outside. We have not used a strip of felt as a "pseudomedia" as we have had the experience of reoperating on a patient from another institution with collapse of the intimal layer away from this pseudointima. Two layers of felt provide a very solid and hemostatic target for both the proximal and distal anastomoses. When we construct this sandwich, we run a horizontal mattress 4-0 Prolene suture being sure that the native tissue itself extends up above the limits of the sandwich. The greatest care is actually with creating this mattress stitch such that the subsequent anastomosis of the graft to the felt sandwich can be performed quickly being assured that if one has both layers of the felt, one also has both layers of the aorta.

***Type I and II/Type A Chronic Dissections.*** Chronic type A dissections should be repaired expeditiously, but not emergently. In the setting of chronic dissection, one has the same options available as in the treatment of chronic aneurysmal disease. Very frequently these patients will have significant aneurysmal dilatation of the arch as well as the ascending aorta. In this instance, we have adopted axillary cannulation and individual graft reconstruction of the brachiocephalic vessels as advocated by Kazui.[32] The individual brachiocephalic reconstructions are actually quicker to perform than a Carrel island patch and are also easier to repair if there is any bleeding from the anastomotic sites (Fig. 41-13). If there is an enlargement of the arch and upper descending thoracic aorta with relatively normal diameter aorta at the hiatus, we have adopted the transverse thoracosternotomy approach advocated by Kouchoukos[33] rather than the two-stage elephant trunk technique (Fig. 41-14). We prefer this even to the elephant trunk with subsequent endograft repair as it provides a secure conventional reconstruction and affords the ability to bevel the distal anastomosis, preserving as many intercostal vessels as possible. We have been concerned about the risk of paraplegia with extensive coverage of the descending thoracic aorta with endografts and see no advantage to the two-stage procedure even if the second stage is performed endovascularly.

***Type III/Type B Acute Dissections.*** In the setting of acute type B dissection, if operative intervention is required, we have preferred the use of circulatory arrest over left heart bypass. Provided there is not significant aortic regurgitation, this provides outstanding neurologic protection. It also affords one an excellent opportunity to perform a precise and secure proximal anastomosis to fragile tissues immediately distal to the left subclavian artery. Furthermore, in the setting of a type B dissection, all of the intercostal vessels are typically patent, which means that, under left heart bypass, all will be back-bleeding significantly. This can be dealt with by segmental clamping and quick hands, but a surprising amount of blood can be lost in a short period of time this way

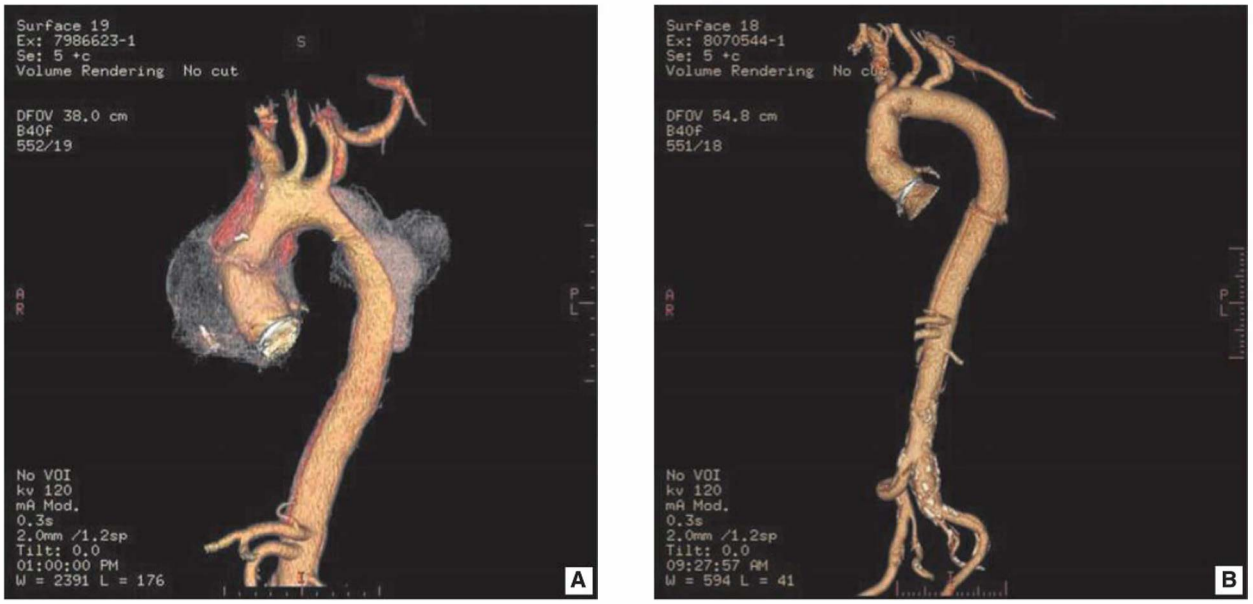



**FIGURE 41-14** A patient with chronic dissection and pseudoaneurysms at both proximal and distal anastomoses: preop (**A**) and postop (**B**). Glue had been used at both anastomoses.

and all shed blood is washed in the cell saver and the clotting factors are lost. Circulatory arrest also permits careful assessment of intercostal vessels to be reimplanted if that is your choice. It also permits careful assessment of the pathogenesis of the dissection, with inspection for the presence of a PAU. Recall that PAUs are more common in the distal thoracic aorta. Approaches that focus on replacement only of the proximal thoracic aorta may leave the PAU untreated.

With circulatory arrest, we have felt comfortable replacing the upper two-thirds of the descending thoracic aorta with a beveled anastomosis down to the diaphragm such that most of the thoracic aorta is extirpated. We believe that this may reduce the need for subsequent operative interventions as compared with replacement of only a very short segment immediately distal to the subclavian artery (Fig. 41-15).

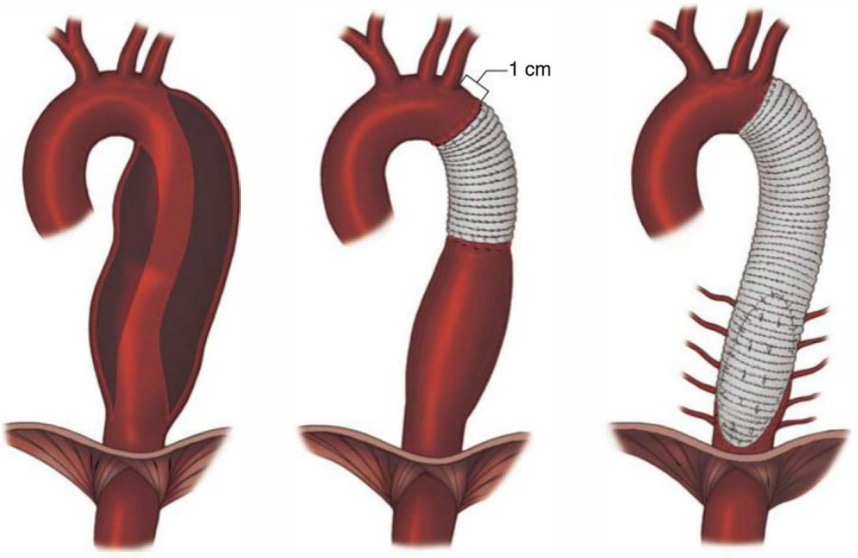



**FIGURE 41-15** When operating on an acutely dissected descending thoracic dissection under circulatory arrest, we have made an effort to extirpate most of the descending thoracic aorta rather than replacing only a short segment just distal to the subclavian artery. Beveling the distal anastomosis preserves the lower intercostal vessels and minimizes the risk of paraplegia.

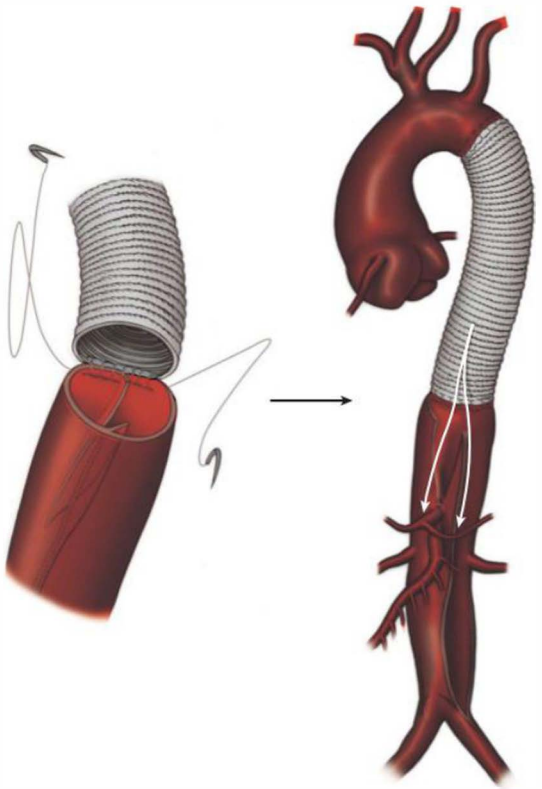


**FIGURE 41-16** Distal fenestration in repair of chronic dissection.

We typically cannulate for cardiopulmonary bypass in this setting either via a Dacron graft on the left axillary artery, via the femoral artery, or occasionally via the left ventricular apex with a femoral arterial inflow cannula. If the femoral artery has been used for inflow, after the proximal anastomosis is performed, we cannulate the graft and perfuse the upper body while we control the remaining intercostal vessels and perform the distal anastomosis at our leisure.

***Type III/Type B Chronic Dissections.*** The indications for surgical intervention on chronic type B dissections are based on aortic diameter and, very occasionally, on the basis of chronic malperfusion. In the setting of chronic type B dissections, we also prefer to use hypothermic circulatory arrest with the same approach as described above. We are always cautious to fenestrate the distal aorta rather than attempting to obliterate the false lumen (Fig. 41-16). Although left-heart bypass is advocated by some of the most prolific surgeons of the thoracoabdominal aorta[34] we were taught to use circulatory arrest.[35] Although the procedure itself takes longer given time to cool and rewarm, and the physiologic insult may be greater, we have been particularly pleased with the level of spinal cord protection afforded. Paraplegia is a devastating complication for the patient, family, and surgeon.

### POSTOPERATIVE CARE

The principles of postoperative care vary depending on the procedure performed. Among patients who have had repair of acute type I/A dissections, there should be aggressive control of hypertension both in the immediate postoperative interval and chronically. Rupture of the descending thoracic aorta after ascending repair occurs. In the chronic phase, there are some data to support the notion that long-term β-blockade and adequate blood pressure control reduce the risk of subsequent dilatation of the residual dissected aorta and accordingly the risk of subsequent operation.

The care of the patient following repair of the thoracic or thoracoabdominal aorta is, frankly, more complex. We have seen a significant incidence of delayed-onset paraplegia, most often associated with hypotension.[36] For this reason, among patients who have had extensive descending thoracic and thoracoabdominal repairs, we tend to have an approach of permissive hypertension aiming for a mean pressure of 85 to 90. In the months following repair, however, one could be more aggressive about blood pressure control. Follow-up scans should be performed at 6 months and then on an annual basis for several years, particularly for younger patients.

## OUTCOMES/PROGNOSIS

Patients surviving an AD require lifelong follow-up. Late survival of patients with dissection continues to be disappointingly below that of the normal population. It is likely that the long-term prognosis depends to a great extent on the adequacy of their follow-up, including aortic surveillance imaging, the rigor with which their blood pressure is controlled, and their access to subsequent surgical treatment should aneurysmal degeneration of the remaining dissected aorta occur. Approximately 30 percent of patients with dissection of the thoracoabdominal aorta—which includes both those with repaired type I/A dissection and those with chronic type III/B dissection—will ultimately come to surgical intervention. Most commonly it is the upper descending thoracic aorta that requires repair.

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## AORTIC DISSECTION BOARD REVIEW QUESTIONS (CHAPTER 41)

1. Which of the following correctly describes a dissection that involves the ascending aorta?
   A. Stanford A and DeBakey II
   B. Stanford B and DeBakey I
   C. Stanford A and DeBakey III
   D. Stanford B and DeBakey III
   E. Stanford A and DeBakey IV

2. Which of the following is true regarding the presentation of aortic dissection?
   A. Occurs more commonly in women
   B. Presents at a younger age in men
   C. Develops more often during the summer months
   D. Occurs most often between the hours of midnight and 6 AM
   E. Penetrating ulcers more commonly involve the ascending aorta

3. The diagnostic imaging modality of choice for aortic dissection is:
   A. Aortography
   B. Echocardiography
   C. MRI
   D. CT
   E. Physical exam

4. Surgical intervention is indicated for which of the following?
   A. Acute type B IMH
   B. Acute type B dissection with diameter greater than 5 cm
   C. Chronic type B dissection with diameter less than 5 cm
   D. Acute type A penetrating ulcer
   E. Infrarenal dissection with extension into right iliac artery

5. Which of the following reduces the risk of reoperation after surgical repair of aortic dissection?
   A. Full root replacement
   B. Open distal anastomosis
   C. Total arch replacement
   D. β-Blocker therapy after operation
   E. Biologic glue reinforcement of proximal suture line

## ANSWERS

1. **Answer: C.** A Stanford type A dissection involves the ascending aorta. DeBakey type I and type II dissections also involve the ascending aorta, with the type I describing a dissection that extends into the descending aorta and the type II describing a dissection limited to the ascending aorta.
2. **Answer: B.** Aortic dissection is more common in men and occurs at a younger age in men. It is more common during the winter months and during the hours of 6 AM to noon. Penetrating ulcers most commonly involve the descending aorta.
3. **Answer: D.** Computed tomography is rapid, highly sensitive and specific, and gives detail on relevant anatomy.
4. **Answer: D.** IMH, PAU, and classic type A dissection are all indications for prompt surgical therapy. The remaining conditions only require surgery if there is associated complication, such as rupture or malperfusion.
5. **Answer: D.** Postoperative control of hypertension with β-blockade has been demonstrated to reduce the incidence of late dilation of the residual aorta, and therefore risk of reoperation. The listed intraoperative strategies have not been conclusively shown to reduce the risk of reoperation.

# 42

# Endovascular Repair of Thoracic Aortic Pathology

*Timothy J. George*
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**KEY CONCEPTS**

- Traditional open surgical repair of thoracic aortic disease is associated with significant morbidity and mortality.
- Endovascular stent-graft therapies have emerged as a minimally invasive approach to treating thoracic aortic pathologies.
- Stent-graft devices consist of membrane material mounted on an expandable metal stented framework.
- Although several imaging modalities have proved useful in planning and executing stent-graft deployment, computed tomography has emerged as the dominant imaging modality because of its wide availability, high resolution, and ability to obtain a variety of three-dimensional reconstructions of the thoracic and abdominal aorta.
- Endovascular stent grafts are deployed through sheaths placed in the common femoral or iliac artery. It is often useful to obtain vascular access through an extension conduit anastomosed to the common iliac artery via a retroperitoneal approach.
- There are four types of "endoleaks," or seepage of blood between the walls of the aorta and/or from graft material.
- Endovascular stent grafts have been used to repair aortic aneurysms, Stanford type B aortic dissections, penetrating atherosclerotic ulcers, and traumatic aortic transections. The results of these repairs are promising but still are accumulating.
- Complications of endovascular stent-graft repairs of the thoracic aorta include spinal cord ischemic injury, retrograde aortic dissection, and iliofemoral arterial injury.

## INTRODUCTION

Traditional open surgical repair of thoracic aortic disease continues to be associated with significant morbidity and mortality. Endovascular stent grafts have emerged as an exciting new technology to treat thoracic aortic pathologies. This minimally invasive approach decreases operative risk by minimizing aortic manipulation, avoiding large incisions and surgical hemorrhage, and circumventing the complications associated with cardiopulmonary bypass. This chapter presents the advantages and challenges of thoracic endovascular aortic repair (TEVAR) of the following pathologies of the thoracic aorta: aneurysm, dissection, penetrating atheromatous ulcers, intramural hematomas (IMHs), and traumatic lesions.

## COMPARATIVE RESULTS OF OPEN REPAIR

Before one begins a review of endovascular repair of thoracic aortic pathology, a review of the current state of open thoracic replacement is required. It is important to draw the clinical distinction between descending thoracic aortic (DTA) replacement and thoracoabdominal aortic (TAA) replacement. The current literature is replete with series of studies of TAA surgery,[1] but series detailing the results of lesser thoracic aortic operations are sparse. In DTA replacement, the duration of renal–visceral ischemia is minimal as the thoracic aortic anastomosis often can be accomplished with less than 30 min of aortic interruption. Indeed, if distal perfusion techniques are employed, renal–visceral ischemia

may be avoided completely. Thus, extrapolating the series detailing TAA replacement to the arena of DTA replacement overestimates the attendant risk of the pathologies now being addressed by endovascular means. Nonetheless, reviewing the literature of thoracic aortic replacement elucidates the risks both avoided (large cavitary incisions and blood loss) and assumed (paraplegia).

The largest series reporting results of DTA surgery for repair of degenerative aneurysms—not thoracoabdominal aneurysms (TAAs)—was published by Coselli and associates in 2004.[2] This series compared the results of surgical repair employing the clamp-and-sew technique with the results of distal aortic perfusion via a left heart bypass (LHB) circuit. Over a 15-year period, 387 patients underwent surgical repair by clamp-and-sew (341 patients; 88.1 percent) or distal perfusion (46 patients; 11.9 percent). Patients requiring profound circulatory arrest because of inability to cross-clamp the aorta (as a result of rupture, large size, or arch involvement) were excluded. Cerebrospinal fluid drainage (CSFD) was used in 24 patients (6.2 percent). The only statistically different preoperative characteristic of the two groups was that the presence of acute dissection was more often associated with the use of LHB ($p = 0.02$). All other variables were similar between the two groups. Intraoperative variables in the two groups were also similar in regard to the extent of the thoracic aorta replaced, the emergent presentation, and reattachment of intercostal arteries. The LHB patients required a longer cross-clamp time ($35.9 \pm 10.4$ min vs $26.9 \pm 9.9$ min, $p < 0.001$), more intraoperative blood products, and had more frequent proximal clamp placement between the left common carotid and the left subclavian than did those treated with clamp and sew (76 vs 54 percent, $p = 0.006$). Postoperative complications were encountered at similar rates regardless of technique. Thirty-day mortality data revealed 2 percent mortality in the LHB group and 2.9 percent mortality in the clamp-and-sew group ($p = 0.1$). Renal failure was noted in 7 percent of patients in both groups. Paraplegia rates were quite similar: a striking 4 percent in LHB patients and 2.3 percent in the clamp-and-sew group ($p = 0.3$). Although the authors hypothesized that patients in the LHB group had a higher risk profile and thus benefited from a subtle protective effect against paraplegia, further propensity analysis failed to support this conclusion. Thus, the application of LHB in patients undergoing thoracic aortic replacement for thoracic aneurysms may be left to the discretion of an experienced aortic surgeon.

Apart from distal perfusion techniques to prevent the dreaded complication of paraplegia, other strategies have been developed to protect the cord from interruption of spinal blood flow. Epidural cooling using an iced saline infusion into the intrathecal space is done to produce a temperature of 25°C to 28°C in the spinal canal, decreasing the neuronal energy requirement.[3] The flow rate into the epidural space may be limited by the measured cerebrospinal fluid (CSF) pressure (CSFP), as the target CSF perfusion pressure [mean arterial pressure (MAP)–CSFP] should be above 40 mm Hg.[4] Admirable paraplegia rates (6 percent) were reported from the Massachusetts General Hospital in its series of over 300 TAA repairs, a series that included a substantial number of high-risk patients many of whom presented acutely with rupture.[5] Commenting on that series, Cambria et al.[5] note that the application of local hypothermia avoids the need for systemic moderate hypothermia and the associated coagulopathy. Besides cooling, other mechanisms have been explored to lower spinal metabolism. Acher et al. reported the use of naloxone therapy and barbiturate-based anesthetics to decrease energy expenditure during the critical period of interruption of spinal blood flow.[6] In their series of 110 thoracic aortic repairs, an admirable 1.6 percent paraplegia rate was observed with this strategy, despite the deliberate oversewing of intercostal arteries in the critical thoracolumbar zone.

CSFD is perhaps the most studied and widely accepted strategy employed for the prevention of paraplegia in thoracic aortic surgery. Experimental data suggest that CSF pressure may rise with proximal aortic clamping and that reducing that pressure may improve spinal perfusion.[3] Thus, placement of a drainage catheter into the subarachnoid space to allow efflux of fluid during the operation and in the postoperative period may benefit the fragile circulation of the spinal cord. Generally, the fluid is able to drain when the CSF pressure exceeds 10 mm Hg as measured at the level of the spine. The beneficial effect of CSFD was demonstrated in a randomized trial comparing repair of type 1 and type 2 TAAs performed with or without CSFD.[7] A total of 145 patients underwent repair, with 76 receiving CSFD and the other 69 undergoing repair without CSFD. Aortic clamp times, LHB use, and the number of intercostal artery reattachments were similar between the groups. Nine patients (13.0 percent) in the control group had paraplegia or paraparesis; in contrast, only two patients in the CSFD group (2.6 percent) had deficits. Overall, CSFD delivered an 80 percent reduction in the risk of postoperative spinal ischemic complications after type 1 and type 2 TAATAA repairs. As CSFD catheter placement is not risk-free, it generally is accepted that CSFD is beneficial in operations in which aortic topography may mandate combined spinal and visceral ischemia, which includes most type 1 and all type 2 TAATAAs.

In addition to paraplegia, patients undergoing complex repairs of the thoracic aorta are at high risk of acute renal failure (ARF), an important contributor to postoperative morbidity and mortality. Unfortunately, the incidence of postoperative ARF is high and the consequences are severe. In a review of 234 consecutive repairs for TAATAAs or descending thoracic aortic aneurysms (DTAAs), Safi et al.[8] reported a 17.5 percent incidence of renal failure, with 15 percent requiring hemodialysis. Although 86 percent of survivors had resolution of their ARF within 30 days, renal failure was associated with a 49 percent mortality rate. Because of the high incidence and serious consequences of postoperative renal failure, many different interventions have been evaluated to reduce this complication. Although intraoperative treatment with mannitol, dopamine, calcium channel blockers, and various free radical scavengers are common, insufficient data exist to support their use. Indirect perfusion of the kidneys

via distal aortic perfusion has been utilized with success, with at least one study demonstrating a protective effect.[8] Several authors have reported results involving direct perfusion of the kidneys via cannulation of the renal ostia. Koksoy et al.[9] have demonstrated that in patients with type II TAATAAs, direct renal perfusion with hypothermic (4°C) lactated ringers resulted in a three-fold reduction in ARF compared with normothermic blood. Perfusion with cold blood, instead of cold crystalloid, does not offer additional benefit.[10]

## Johns Hopkins Approach to Open Thoracic Aortic Replacement

There are a number of approaches to the open replacement of the thoracic aorta. The authors' approach has been described in detail elsewhere[11] and is summarized here. Our operative approach begins with detailed preoperative planning utilizing high-quality imaging, computed tomography angiography (CTA) if possible, to evaluate the aorta for aortic atherosclerotic disease, dense calcifications, and aortic branch ostial disease to properly delineate the optimal sites for proximal cross-clamp, revascularization, and need for renal and/or visceral ostial endarterectomy.

For type I to III TAATAAs, CSFD, and LHB are employed. For type 4 TAATAAs, LHB and CSFD rarely are employed as no data exist to support their efficacy in these groups. The abdominal aorta is exposed via retroperitoneal dissection while the thoracic aorta is approached through a standard, posterolateral incision. The diaphragm is divided in a circumferential fashion to avoid injuring the phrenic nerve. LHB is instituted through the cannulation of the inferior pulmonary vein and an 8-mm Dacron chimney to the left common femoral artery. Distal perfusion is performed with moderate hypothermia (32°C) via a heat exchanger on a Bio-Medicus centrifugal pump. During the opening of the abdominal aorta, the renal artery ostia are flushed with 250 $cm^3$ of cold saline to aid in renal preservation.

To perform aortic reconstruction, the proximal descending aorta is isolated first via a proximal aortic clamp. This anastomosis is followed by subsequent sequential clamping of the aorta during each arterial anastomosis and reimplantation of intercostal, renal, and visceral arteries (Fig. 42-1).

# THORACIC AORTIC ENDOVASCULAR DEVICE OVERVIEW

First-generation stent grafts for repair of thoracic aortic pathology were bulky handmade devices that employed pressed Dacron material hand-sewn onto Gianturco stainless steel stents that necessitated large-diameter sheaths (26F) and stiff delivery systems, often requiring that conduits be sewn onto the iliac or abdominal aorta to accommodate the diameter of the delivery device. Newer-generation devices offer improved flexibility with small introducer systems. The US Food and Drug Administration (FDA) approved the first

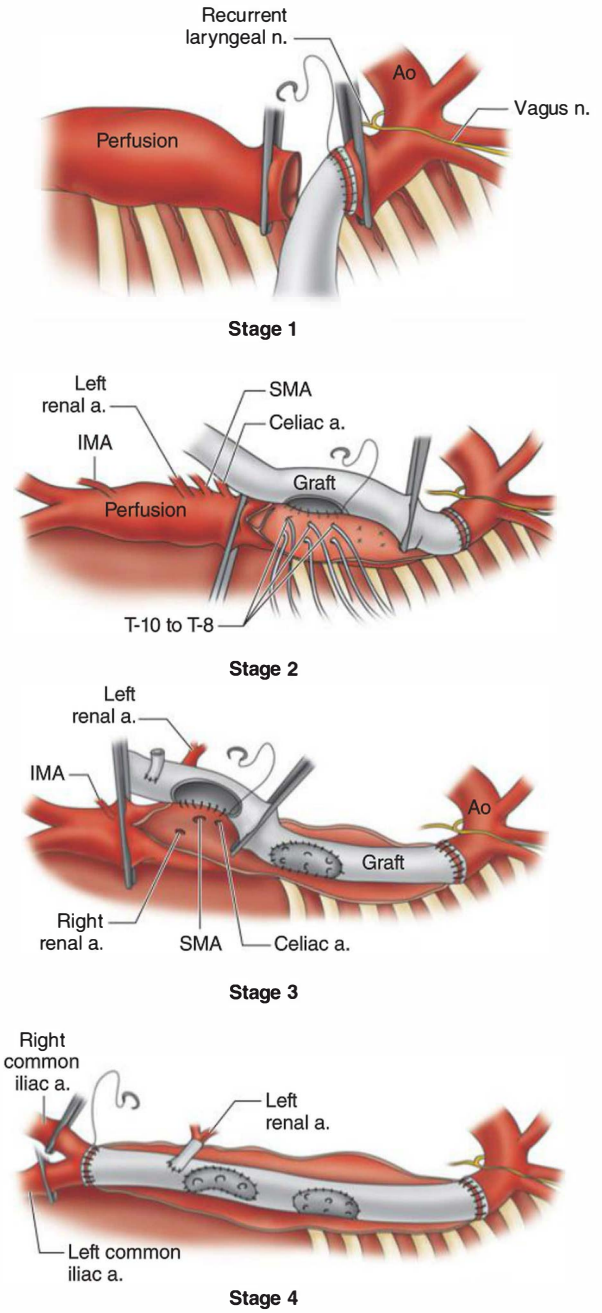



**FIGURE 42-1** Sequential stages of type II TAA repair. In Stage 1, the proximal anastomosis is performed while distal blood flow maintains renal and visceral perfusion. In Stage 2, the graft is clamped distal to the proximal anastomosis while the intercostals are reimplanted. In Stage 3, the graft is clamped distal to the intercostal patch and distal blood flow maintains pelvic perfusion during the renovisceral reconstruction. In Stage 4, the aortic bifurcation is reconstructed. (Reproduced with permission from Black JH 3rd. Technique for repair of suprarenal and thoracoabdominal aortic aneurysms. *J Vasc Surg* 2009 Oct;50(4):936–941. Copyright Elsevier)

**TABLE 42-1: Indications and Sizing Guidelines for FDA-Approved Devices**

| Parameter | TAG | Zenith TX 2 | Talent Thoracic |
|---|---|---|---|
| FDA-approved indication | DTAA | DTAA and PAU | DTAA and PAU |
| Treatable aortic diameters | 23–37 mm | 24–38 mm | 18–42 mm |
| Length of proximal and distal landing zones | ≥20 mm | ≥25 mm | ≥20 mm |
| Percent oversizing to aorta | 6–19% | 10–20% | 18–42% |
| Required sheath delivery size | 20, 22, 24F | 20, 22F | 22, 24, 25F |

DTAA, descending thoracic aortic aneurysm; PAU, penetrating aortic ulcer.

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endovascular device for the treatment of degenerative thoracic aneurysms in late 2004.

There are currently three FDA-approved devices commercially available for endovascular repair of the thoracic aorta: the TAG endoprosthesis (W.L. Gore and Associates, Inc, Flagstaff, AZ), the Zenith TX2 TAA Endovascular Graft (Cook, Inc, Bloomington, IN), and the Talent Thoracic Stent Graft System (Medtronic Vascular, Santa Rosa, CA). All three devices, the TAG, the Zenith, and the Talent endoprostheses, consist of a series of self-expanding metal stents (either nitinol or stainless steel) affixed to tube grafts [made of polytetrafluoroethylene (PTFE), polyester, or woven graft, respectively]. Although the TAG device consists of single tube graft, the TX2 and the Talent are designed as two-piece systems with proximal and distal ends so that a combination of multiple proximal pieces and a distal piece can be utilized depending on the characteristics of the patient's individual aorta. In addition, the proximal component of the Talent device consists of several uncovered nitinol springs that allow the device to be deployed across a vessel (the left subclavian or left common carotid artery) without impeding blood flow. The treatable lengths and diameters for each device are listed in Table 42-1.

## DIAGNOSIS OF THORACIC AORTIC PATHOLOGY

A wide range of diagnostic tests are helpful in confirming suspected thoracic aortic pathology, including chest radiography, aortography, transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE), magnetic resonance imaging (MRI), computed tomography (CT), and recently serum biomarkers. The benefits and limitations of each of those methods are reviewed below, along with their applicability to aneurysmal and dissection pathology.

### Plain Radiography

Classically, widening of the cardiac or aortic silhouette is cited as indicative of aortic disruption, along with pleural effusions and the displacement of aortic calcifications. Specifically, widening of the aortic silhouette was found in 60 to 90 percent of cases of aortic dissection by Hagan and coworkers in their review.[12] However, chest radiography has limited specificity and sensitivity.

### Aortography

This modality has both high sensitivity (86–88 percent) and high specificity (75–96 percent) for the diagnosis of aortic dissection.[13] Findings suggestive of dissection include distortion of the normal contrast column, flow reversal or stasis in a false channel, failure of major branches to fill, and aortic valvular regurgitation.[13] For the diagnosis of thoracic aortic aneurysm and treatment planning, aortography may improve the accuracy of length measurements of intended aortic seal zones (Fig. 42-2). In addition, aortography may be of benefit in defining aortoiliac occlusive disease, which may require angioplasty or a planned conduit for access for the stent-graft delivery. Nonetheless, enthusiasm for this modality is tempered by the potential for diagnostic confusion about malperfusion after pressurized injection, the risk of contrast nephropathy, the time delay to diagnosis, and the expense.

### Transthoracic Echocardiography and Transesophageal Echocardiography

TTE has a sensitivity of 35 to 80 percent and a specificity of 40 to 95 percent for the detection of aortic dissection,[14] whereas the sensitivity of TEE is reportedly as high as 98 percent, with 63 to 96 percent specificity.[15] TTE may be limited technically by body habitus, emphysema, and narrow intercostal spaces. Although TEE is more invasive, it expands the diagnostic ability of echocardiography, potentially demonstrating entry tear sites, flow within the false lumen, involvement of the arch or coronary arteries, degrees of aortic valvular regurgitation, and pericardial effusions. However, one must be mindful of its limitations in imaging the anatomic blind spot in the distal ascending aorta and arch secondary to the air-filled trachea and left mainstem bronchus. In addition, TEE cannot image aortic pathologies past the diaphragm.

### Magnetic Resonance Imaging

MRI has unparalleled sensitivity and specificity for detecting aortic pathology, for instance, 95 to 100 percent for

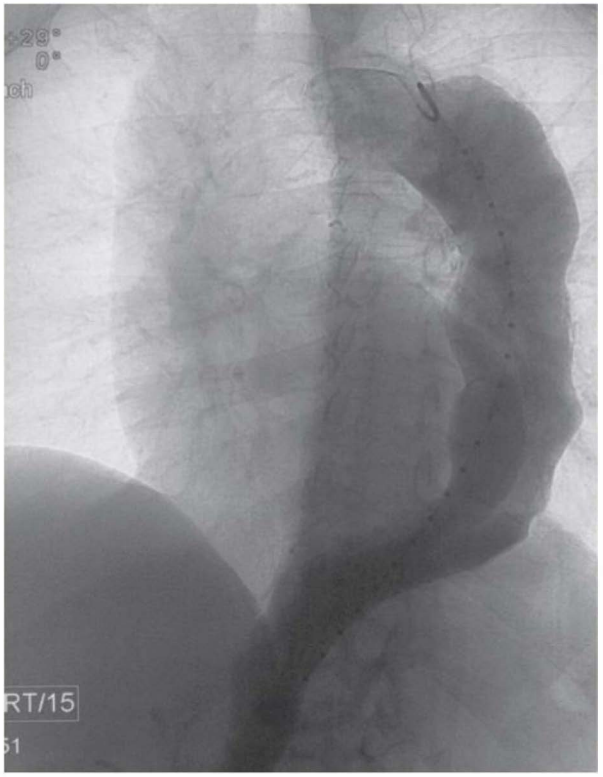


FIGURE 42-2 Angiography is a vital adjunct to preprocedural planning.

dissection.[16] Recent advances in three-dimensional (3-D) reconstruction of gadolinium-enhanced magnetic resonance angiography (MRA) are beneficial in planning thoracic aortic stent-graft treatment in patients whose comorbidity profile includes renal insufficiency. However, this enthusiasm must be tempered by the realities of long examination times, inability to monitor critically ill patients, expense, and lack of immediate availability. Moreover, MRI is contraindicated for patients with implants or pacemakers.

## Computed Tomography

CT offers multiple benefits and is the most commonly used diagnostic test in patients with suspected aortic pathology. Readily available, CT scanning carries a sensitivity of 83 to 95 percent with a specificity of 87 to 100 percent for the detection of acute aortic dissection.[17] This modality can be particularly helpful in examination of the true versus the false lumen. A slit-like compressed true lumen should heighten suspicion for branch vessel compromise and malperfusion syndrome substantially (Fig. 42-3). In addition, CTA has evolved so that multiple reconstructions can be created from the source axial images, rendering this diagnostic modality vital for preoperative planning.

## Serum Biomarkers

Serum biomarkers, particularly D-dimer, represent an emerging diagnostic tool for detecting aortic dissection, particularly for screening patients with chest pain in whom high-quality, axial imaging would be prohibitively expensive. When the aortic media tears, the extrinsic pathway is triggered resulting in the cross-linking of fibrin. D-dimer is a degradation product of this cross-linking reaction and thus represents a potential biomarker of aortic dissection. A cutoff value of <500 ng/mL can be used to rule out aortic dissection, yielding a negative likelihood ratio of 0.07 and a negative predictive value of 95 percent.[18] However, up to 18 percent of patients with confirmed aortic dissection will not have a D-dimer level greater than 400 ng/mL[19] likely secondary to the variability of serum levels based on the time since dissection. Thus it is currently most useful to rule out patients who are considered low risk.

# IMAGING FOR PLANNING THERAPY

Endovascular repair of thoracic aortic pathology requires facility with the interpretation of axial imaging such as CTA and MRA to inspect aortic topography for device insertion and fixation. In addition, planning of thoracic aortic endografting may be aided by conventional diagnostic arteriography, using both subtracted and unsubtracted techniques, especially when 3-D imaging cannot be obtained from available axial data. A key tenet of thoracic aortic endovascular repair is the understanding that device selection and operative planning should be confirmed and verified to the greatest extent possible preoperatively as errors in device measurements often translate into immediate treatment failures.

Insertion planning for endovascular devices requires a thorough understanding of the aortic diameters at the proximal and distal sealing sites as measured from outer wall to outer wall. The indications and sizing guidelines for the current FDA-approved devices are summarized in Table 42-1.

Oversizing the graft too aggressively may place undue forces on the aortic endograft and result in migration or collapse of the entire graft.[20] The length of proximal fixation should be more than 20 mm (or 25 mm in the case of the Zenith device) with an acceptable aortic diameter throughout this seal zone. If an adequate proximal fixation length is not immediately obtainable, the left subclavian artery (LSA) can be crossed and excluded with little consequence to the patient (mean left arm pressure decreased, with few symptoms); if the patient has a prior left internal mammary-to-coronary bypass, a left-carotid-to-left-subclavian bypass is required to maintain coronary circulation before coverage. Further encroachment into the arch generally requires salvage of the left common carotid circulation by a prior carotid–carotid bypass. If excessive tortuosity is encountered in either fixation zone, a longer seal length of up to 30 mm may be needed to prevent blood from escaping around the

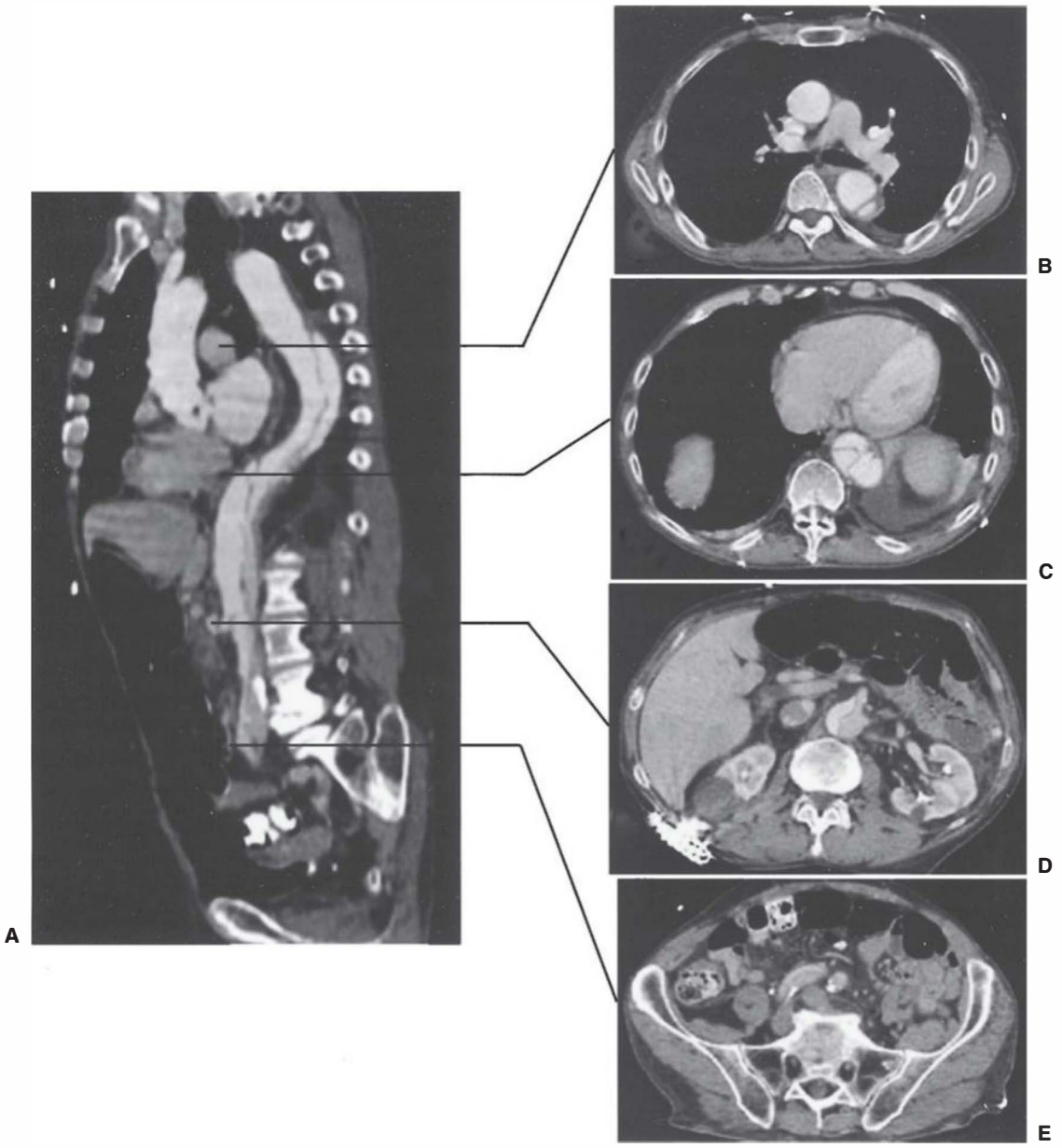



**FIGURE 42-3** Three-dimensional helical computed tomography has a sensitivity of 83 to 95 percent and a specificity of 87 to 100 percent for the detection of acute aortic dissection.

ends of the stent (type 1 endoleak). When multiple devices are required to cover long lengths of aortic pathology, each piece should be made to overlap 3 to 5 cm with the neighboring endograft. The distal aortic seal zone is usually cephalad to the celiac axis.

A common theme in complications of aortic endografting is the occurrence of damage to access vessels such as the common femoral and iliac arteries. Therefore, if the measured diameter of an intended access vessel is demonstrated to be less than 8 mm, serious consideration should be given to a surgical conduit. To create a conduit, 10-mm Dacron conduits generally are anastomosed to the common iliac or abdominal aorta via a miniflank incision with retroperitoneal exposure of the vessel. In particular, severe calcification of an access vessel may increase the risk of tear, perforation, dissection, or frank rupture. It is not uncommon for such iatrogenic injuries to become obvious when the device sheath is being withdrawn, not at the time of sheath insertion. As the device sheath is removed, the obturation of the injury is relieved and hemorrhage ensues.

## IMPLANTATION TECHNIQUE

The procedure of aortic endografting for thoracic aortic pathologies should be performed in an operating room with a high-resolution digital imaging system and a radiolucent table. The choice of anesthetic generally is based on preoperative cardiac risk stratification and may include local, epidural, and general anesthesia. The application of CSF drainage should be considered when coverage of the entire thoracic aorta is planned or if a prior abdominal aortic aneurysm (AAA) repair has been performed. Grafts are inserted via cutdown on the intended access vessel, most commonly the right common femoral artery. After this surgical exposure, systemic anticoagulation is achieved, using heparin to maintain an activated clotting time (ACT) greater than 250 s. An angiographic catheter is inserted percutaneously via the opposite common femoral artery or brachial artery to the level of the aortic arch. Using digital subtraction angiography, aortic arch or thoracic aortic angiography is performed to determine the approximate positioning of the endoprosthesis. To view the landing areas in the arch, it often is necessary to view the arch with a 60-to-90 degree left anterior oblique (LAO) projection. To view the distal seal zone, a similar steep, nearly lateral projection best depicts the level of the celiac axis (Fig. 42-4).

To minimize manipulation, particularly in the arch, the final diagnostic studies before deployment should be performed with the device nearly in place; the stiffness of the wires and delivery systems may alter the course of the aortic arch and affect the landmarks being used to mark the proximal limits of deployment. "Road-mapping" techniques or "fluoro-fade" may improve operator accuracy in proximal fixation. Maneuvers to minimize stroke include flushing of all air from the device sheaths and lumens carefully. Also, manipulation of stiff wires into and from the arch should be done carefully under fluoroscopic guidance. After deployment, fixation should be improved by using a large-diameter compliant occlusion balloon to maximize apposition of the stent graft to the aortic seal zones and regions of device overlap in a distal-to-proximal order (Fig. 42-5). The access sheath is removed carefully, with attention paid to MAP as an early indicator of hemorrhage from iatrogenic insertion injury. If a tear in a vessel is suspected, the sheath can be reintroduced to obturate the injury. If the sheath will not pass, an occlusion balloon can be passed proximal to the injury and inflated to achieve vascular control. Frank transections usually require a flank incision and reconstruction, whereas small tears or dissections often are salvaged by endovascular stent placement without conversion.




**FIGURE 42-4** Distal aortic projection with a 68 degree left anterior oblique view often is required for proper visualization of the celiac axis for sizing. The figure shows a larger graduated device posterior to the pigtail catheter.




**FIGURE 42-5** Deployed stent graft.

### Johns Hopkins Approach to Thoracic Aortic Stent Grafting

In light of the preponderance of iatrogenic access injuries, the authors aggressively apply retroperitoneal conduits via a flank incision. Most patients undergo general anesthesia both for flexibility of access approach and to avoid patient movement at critical imaging moments. The operations are performed in an endovascular operating room with a ceiling-mounted imaging device.

## THORACIC ENDOVASCULAR AORTIC REPAIR OF ANEURYSMS

With an estimated incidence of 6 to 10 cases/100,000 person-years, a thoracic aortic aneurysm carries a substantial risk of mortality. Coady and associates[21] found a 27.9 percent total incidence of rupture or dissection for DTAAs larger than 6.0 cm. The long-term survival of patients with untreated DTAAs at 1 and 5 years was 88 and 6 percent, respectively.[21] As with AAAs, the yearly risk of rupture or dissection for DTAAs has been found to correlate with size: 2 percent for small aneurysms, 3 percent for aneurysms 5.0 to 5.9 cm, and 6 percent for those equal to or larger than 6.0 cm. The risk of death along with rupture and dissection increases markedly at 6.0 cm: 6.5 percent yearly for aneurysms 5.0 to 5.9 cm but 14.1 percent for those equal to or greater than 6.0 cm.[22]

The results of TEVAR in DTAAs are summarized in Table 42-2.[23–26] In the table, endoleak refers to the seepage of blood between the previously sealed walls of the aorta and graft material. Endoleaks are divided into four types: Type I endoleaks occur as a consequence of a poor seal between the aorta and[23] the proximal or distal attachment sites of the graft, type II endoleaks are characterized by back bleeding from branch vessels, type III leaks involve blood excursion between multiple components of grafts, and type IV endoleaks occur when blood transgresses from the lumen through the material of the graft itself.

The use of stent grafts to treat DTAAs was pioneered by Dake et al. in 1994.[25] Although endovascular repair previously had been described for AAAs, subclavian artery aneurysms, arteriovenous fistulas, and femoral occlusive disease, this group from Stanford extended the technology to the thoracic aorta. Their series of 13 patients had 100 percent technical success and no mortality nor paraplegia. The authors reported that two patients had "small patent proximal tracts communicating with the aneurysm" that resolved over the ensuing months and that two more patients required a second procedure to eliminate "residual filling from either a proximal communication or a distal communication," presumably type I endoleaks (30.8 percent). In light of those promising early results, the authors advocated endovascular treatment for highly selected patients.

The first long-term outcomes were reported by Makaroun et al.[26] who reported the midterm follow-up results of the Gore TAG trial. This trial compared 191 patients who underwent endovascular repair of DTAAs with the TAG device (51 patients were enrolled after redesign of the endograft device) to 94 patients who underwent traditional, open repair. At 5-year follow-up, patients undergoing endovascular treatment had a decreased rate of aneurysm-related mortality (2.8 vs 11.7 percent, $p = 0.008$) and a similar rate of all-cause mortality (68 vs 67 percent, $p = 0.433$). TEVAR was associated with a lower incidence of major adverse events in the first postoperative year (42 vs 77 percent, $p < 0.001$) and these patients were less likely to have bleeding, pulmonary, renal, neurologic, or wound complications; however, TEVAR patients were more likely to have vascular complications at 5 years. Endoleaks, predominantly type I, occurred in 21 percent of patients who underwent endovascular surgery, and 3.6 percent patients in the endovascular group required postoperative reintervention. Only one patient required conversion to an open procedure 73 days after endovascular treatment secondary to the detection of an aortoesophageal fistula. At 5 years, the aneurysmal sac size had decreased in 50 percent of patients and increased in only 19 percent. In addition, at 5 years, there were no ruptures, no stent-graft collapse, and only one incident of significant stent migration. These encouraging long-term results lead the authors to conclude that TAG thoracic endografting is not only a safe and effective method of repairing DTAAs, but superior to open repair in terms of aneurysm-related morality.

Although initial trials were performed with the TAG device, additional trials have since followed utilizing other devices. Matsumura et al.[23] evaluated the Zenith TX2 device, comparing 160 patients who underwent endovascular repair

**TABLE 42-2: Results of Endovascular Repair of Thoracic Aortic Aneurysms**

| | Dake (1994) | Czerny (2004) | Makaroun (2008) | Matsumura (2008) |
|---|---|---|---|---|
| Technical success | 100% | 94.4% | 98% | 98.8% |
| 30-day mortality | 0% | 3.7% | 2.1% | 1.9% |
| Complication rate | 7.7% | 1.9% | 57.9% | 41.9% |
| Paraplegia | 0% | 0% | NR | 1.25% |
| Endoleak | 30.8% | 28.9% | 21% | 13% |
| Mean follow-up | 11.6 months | 38 months | 37 months | 12 months |
| Long-term survival | 100% | 92.6% | 68% | 91.6% |

of their DTAA to 70 patients who underwent traditional, open replacement. Although the 30-day and 1-year survival rates were similar between the endovascular and open groups, patients undergoing TEVAR had fewer cardiovascular, pulmonary, and vascular adverse events (41.9 vs 68.9 percent, $p < 0.01$). Endovascular repairs were complicated by a similar rate of reintervention as those undergoing open repair. In addition, at 1 year, there were no aneurysm ruptures, a 3.9 percent incidence of endoleaks, and a 2.8 percent incidence of graft migration. This study demonstrated that endovascular repair with the TX2 device is a safer and equally effective alternative to open surgical repair for DTAAs.

The overwhelming majority of large studies that have evaluated endovascular repair of thoracic aneurysms have examined the outcomes of elective repairs. Recently, however, Jonker et al.[27] conducted a meta-analysis of endovascular repair of ruptured DTAAs. This study examined 224 patients, 64 percent treated with endovascular repair and 36 percent with open repair. TEVAR was associated with decreased 30-day mortality (19 vs 33 percent, $p = 0.016$) and a decreased incidence of perioperative myocardial infarction. Notably, four patients treated with TEVAR who were alive at 30 days died because of exsanguination due to rupture of the stented aneurysm or the adjacent aortic segment. Another patient died due to an aortobronchial fistula. In contrast, there were no aneurysm-related deaths in the open group during follow-up. Although TEVAR of ruptured DTAAs is associated with a lower 30-day mortality compared with open repair, it is also associated with more aneurysm-related deaths on long term follow-up.

With an increasing focus on the costs associated with health care delivery, increased attention is being paid not only to the effectiveness of novel therapies such as endovascular repair of DTAAs, but also to their cost-effectiveness. Although several studies including those mentioned above demonstrate improved survival and shorter length of stay for TEVAR versus open repair, few studies have examined the differences in cost. Recently, Arnaoutakis et al.[28] reported that while TEVAR demonstrates improved mortality and shorter intensive care unit (ICU) and overall length of stay, it is associated with similar total charges despite high-device costs (US $61, 909 vs US $64, 531, $p = 0.40$).

## THORACIC ENDOVASCULAR AORTIC REPAIR OF DISSECTIONS

Acute aortic dissection is the most common catastrophe of the aorta, with an annual incidence of 5 to 30 cases/million people/year.[12] Age, hypertension, and structural abnormalities of the aortic wall contribute to the actual incidence within a population.[12] A male:female ratio of 5:1 is consistent across many series,[29] the incidence of dissection peaks at 50 to 60 years of age for type A and at 60 to 70 years for type B,[12] and hypertension contributes to 70 to 80 percent of cases.[30]

Despite marked treatment advancements since Shekelton's first efforts in the early 1800s, acute aortic dissection remains a lethal affliction. In the International Registry of Acute Aortic Dissection (IRAD) study from 2000, overall mortality stood at 27.4 percent, ranging from 26 percent for patients undergoing graft placement for ascending dissections to 58 percent for those managed medically. Mortality for patients with descending dissections stood at 10.7 percent for medical treatment compared with 31.4 percent for surgery.[12] Similarly, Meszaros et al.[31] found that 21 percent of patients succumbed before hospital admission. Each hour left untreated increases the risk of death: 22.7 percent within 6 h, 50 percent within 24 h, and 68 percent within the first week. When the dissection involves the ascending aorta, mortality follows rupture into the pericardium, dissection of the coronary ostia, and acute aortic regurgitation. In dissection of the descending aorta, mortality may result from visceral or extremity vessel obstruction or from aortic rupture.

Like DTAAs, aortic dissections may result from a myriad of pathologic processes. For instance, bicuspid aortic valves and the resultant aortic root dilatation are a well-established risk factor that is found in 7 to 14 percent of all aortic dissections.[12,30] Other aortic diseases ranging from the genetic to the congenital contribute to dissection: Marfan syndrome, Ehlers–Danlos syndrome, Turner syndrome, Noonan syndrome, coarctation of the aorta, annuloaortic ectasia, aortic arch hypoplasia, and aortic arteritis.[32] Common to many of those diseases is degeneration of the medial collagen and elastin, leading to diminished structural integrity of the aortic layers.

Beyond these diseases, medial degeneration seems to arise in dissection patients as a consequence of aging or hypertension; repetitive or excessive $dP/dt$ (change in pressure over change in time) slowly contributes to the breakdown of medial collagen and elastin.[33]

The acute versus chronic differentiation occurs at diagnosis 2 weeks after the initial onset of symptoms. Anatomically, two classification schemes prevail: the one proposed by DeBakey and colleagues in 1965 and the Stanford classification, although the former has more widespread use[34]:

- Type I: Dissection originates in the ascending aorta and extends through the aortic arch and into the descending aorta and/or abdominal aorta for a varying distance.
- Type II: Dissection originates in and is confined to the ascending aorta.
- Type III: Dissection originates in the descending aorta and is limited to that structure in type IIIa; type IIIb involves descending and variable extents of the abdominal aorta.

Daily and colleagues developed the Stanford classification scheme in 1970.[35] That system divides dissections into those originating in the ascending aorta (Stanford type A; DeBakey types I and II) and those confined to the descending aorta (Stanford type B; DeBakey types IIIa and IIIb). Here the discussion is limited to Stanford type B.

Over 93 percent of patients with acute aortic dissections present with pain, with 85 percent experiencing an abrupt onset.[12] Because dissection may occur anywhere along the course of the aorta, the precise location of the

pain varies: anterior chest pain radiating to the arm or jaw for type A dissections compared with back or intrascapular region for type B processes.[12,30] Complaints of abdominal pain in this setting raise the specter of mesenteric vascular compromise. True to traditional teachings, patients characterize the pain as "the worst ever" in 90 percent of cases, with a sharp (68 percent), ripping or tearing (50 percent), or migratory character (19 percent).[12] Although syncope presents in less than 3 percent of patients with acute dissection, it is a harbinger of a complex and often fatal course.[12] Patients who present with syncope are more likely to have a type A than a type B dissection (19 vs 3 percent, $p < 0.001$), more often have cardiac tamponade (28 vs 8 percent, $p < 0.001$), may have suffered a stroke (18 vs 4 percent, $p < 0.001$), and are more likely to die in the hospital (34 vs 23 percent, $p = 0.01$).[36] Spinal cord ischemia occurs in 2 to 10 percent of type B dissections as a consequence of the interruption of intercostal vessels.[37] Less commonly, patients may experience neuropathies from direct compression of a peripheral nerve: paresthesias from lumbar plexopathy, hoarseness from compression of the recurrent laryngeal nerve, and Horner syndrome secondary to sympathetic ganglion compression.

The natural history of aortic dissection predicts progression to aneurysmal dilatation. In fact, 20 percent of TAAs are attributable to chronic dissection in most series.[1] Factors that contribute to this evolution to aneurysm include poorly controlled hypertension, a maximal aortic diameter equal to or greater than 4 cm in the acute phase, and continued patency of the false lumen.[38] Ten to twenty percent of those with dissection subsequently have late rupture of the aneurysm.[39] Moreover, aneurysms that result from chronic dissection tend to be more extensive and occur in younger patients compared with degenerative aneurysms. Open surgical repair of type B dissections rarely is indicated emergently, except in the setting of threatened or actual rupture at the aortic intimal tear. In light of the substantial morbidity and complications associated with extensive aortic replacement in the emergent setting, some have argued for the abandonment of central aortic repair in the setting of type B dissection. The surgical results of open central aortic repair for dissection have not been overwhelming as 25 to 50 percent of these patients persistently have false lumen flow,[40] and surgeons have variable success in relieving distal malperfusion. More important, perioperative mortality ranges from 6 to 67 percent.[41]

Endovascular repair may emerge as a definitive and superior method to treat aortic dissection. An intuitive advantage of endovascular treatment is its ability to obliterate the false lumen by sealing the aortic tear with an aortic endograft. Continued patency of the false lumen has been noted to lead to aneurysmal dilatation.[38] Certain technical aspects of stent-graft placement merit emphasis. First, it is ill advised to place uncovered stents over the site of the entry tear within the proximal true lumen. It is not known whether an acutely dissected intimal flap can tolerate aggressive oversizing of the proximal aorta with a stent. Furthermore, the radial force of a stent may overdistend the true lumen in tortuous portions of the aorta. By these two mechanisms, deployment of such uncovered stents may cause aortic rupture, as has been confirmed in animal studies.[42]

A summary of select trials using stent grafts for aortic dissection is provided in Table 42-3.[41,43–47] Dake et al. reported outcomes of stent-graft therapy for type B dissections after their initial experience with homemade devices in 15 patients.[43] Two patients required deployment of a second stent because of residual flow in the false lumen from proximal or distal communication. In that initial series, three patients died (20 percent): two from false lumen rupture hours to days after stent grafting and the third from sepsis 7 days later, apparently as a result of malperfusion syndrome. Their complication rate stood at 20 percent, including gut infarction, leg gangrene, pneumonia, and renal failure. However, stent grafting was successful in achieving complete thrombosis of the false lumen in 12 of the 15 surviving patients. These authors advocated stent grafts

**TABLE 42-3: Results of Endovascular Repair of Stanford Type B Aortic Dissections**

| | Dake (1999) | Nienaber (1999) | Bortone (2002)—Immediate Treatment | Bortone (2002)—Delayed Treatment | Xu (2006) | Szeto (2008) | Parker (2008) |
|---|---|---|---|---|---|---|---|
| Technical success | 100% | 100% | 100% | 57% | 95.2% | 97.1% | 95% |
| Mortality | 20% | 0% | 0% | 7% | 3.2% | 2.8% | 9% |
| Complication rate | 20% | 0% | 15% | | 9.5% | 29% | 10.2% |
| Paraplegia | 0% | 0% | 0% | 0% | 0% | 2.8% | 1.9% |
| Endoleak | 20% (immediate); 7% (1 month) | 0% | 0% | 0% | NR | NR | NR |
| False lumen thrombosis | 83% (immediate) 100% (3 months) | 83% (immediate) 100% (3 months) | 100% | | 98.4% | 74.1% | NR |
| Mean follow-up | 10.9 months | 1 year | 9.7 ± 8.5 months | | 11.7 months | 13 months | 20 months |

NR, not reported.

to protect against end-organ ischemia but also emphasized the importance of promptly sealing an intimal tear to preclude progression to aneurysm.

Nienaber et al. published their early endovascular experience concurrently with the study mentioned above.[44] Their trial compared 12 consecutive patients with type B dissections treated with stent grafts to matched controls who were treated operatively. Whereas Dake and co-investigators had used custom-designed stents, Nienaber used commercially available components with uncovered proximal fixation. Although surgical treatment accrued 33 percent morbidity ($p = 0.09$) and 42 percent mortality ($p = 0.04$), those with stent grafts experienced no morbidity or mortality within 12 months. Ten of the twelve patients experienced immediate thrombosis of the false lumen after graft deployment, with the remaining patients demonstrating thrombosis at 3-month follow-up. Compared with surgical therapy, those undergoing endovascular treatment had a shorter stay in the ICU ($p < 0.001$), a shorter hospital course ($p < 0.001$), and lower overall mortality ($p = 0.04$). That group concluded that not only may stent-graft treatment of thoracic aortic dissections offer substantial cost savings, it is also associated with lower morbidity and mortality than open repair.

More recently, Xu and colleagues[45] reported their experience from 2001 to 2005 of 63 consecutive patients with type B thoracic aortic dissection treated with TEVAR. In this series, the perioperative mortality was 3.2 percent with a 4-year actuarial survival of 89.4 percent. In this group, TEVAR was complicated by the induction of ascending dissection during two procedures. One year post procedure, CTA showed a decrease in the size of the false lumen (average diameter decrease of 11.2 percent) and an increase in the true lumen in most patients. In addition, complete thrombosis of the false lumen was achieved in over 98 percent of patients. The authors concluded that early and midterm results demonstrate that TEVAR is an effective means of treating acute type B dissection of the thoracic aorta.

A common indication for open operation on a type B dissection remains the potential for life-threatening complications including renal and visceral malperfusion and rupture or imminent rupture. Although open replacement has frequently been undertaken for these indications, the role of endovascular treatment is less well characterized. Szeto and colleagues[46] therefore reported their institutional experience with emergency TEVAR in 2008. From 2004 to 2007, 35 patients with acute complicated type B aortic dissection were treated with TEVAR. In their series, 51 percent of patients had rupture and 49 percent had malperfusion of the mesentery, kidneys, and/or lower extremities. Overall, they reported only one perioperative mortality secondary to failure to cover the primary tear site resulting in free rupture on postoperative day 3. At 13-month follow-up, there was one additional death, and three patients required aortic reintervention, one for dissection of the ascending aorta, one for persistent endoleak, and one for a sinus of Valsalva aneurysm. In acute life-threatening type B aortic dissection, TEVAR is a safe and effective means of treatment; however, sufficient coverage of the primary dissection site is crucial to prevent complications.

Although most series evaluating endovascular treatment of aortic dissection are small, a recent meta-analysis of the literature was undertaken by Parker and colleagues[47] to further characterize this patient population. This analysis examined 942 patients who presented with acute type B aortic dissection and were treated with TEVAR. Perioperative mortality was 9 percent, and 20-month survival was 88 percent. Late aortic rupture occurred in 0.8 percent of patients while 7.6 percent of patients required endovascular reintervention and 2.8 percent of patients required open surgical reintervention. The early, favorable outcomes in this study of many different centers suggest that TEVAR can be broadly applied to patients with aortic dissection with acceptable outcomes.

### Johns Hopkins Approach the Management of Aortic Dissection

At the Johns Hopkins Hospital, we approach the management of aortic dissection as outlined in Figure 42-6. In general, endovascular repair is reserved for patients with an acute presentation and evidence of malperfusion.

## HYBRID APPROACH TO THORACOABDOMINAL AORTIC ANEURYSMS

TAAs continue to represent one of the most challenging pathologies encountered by vascular surgeons. This condition is highly lethal when managed medically but accompanied by significant morbidity and mortality when managed surgically. Although significant progress has been made with traditional surgical management, with large institutional series demonstrating mortality rates less than 10 percent, national series continue to demonstrate a mortality rate closer to 20 percent with a 15 percent rate of permanent paraplegia and 20 to 30 percent incidence of renal failure.[48,49]

Given the high morbidity and mortality associated with the traditional, open repair of TAAs, surgeons have investigated various endovascular approaches to this problem. The most common technique to circumvent an open TAA repair is the utilization of a hybrid procedure combining open visceral and renal debranching with endovascular aortic stenting. Theoretically, hybrid procedures avoid the need for aortic cross-clamping, single lung ventilation, and partial LHB.[48]

Early results of hybrid TAA procedures were promising. Black et al.[49] reported their 29-patient series in 2006. They found a perioperative mortality of 13 percent and no paraplegia. However, the results of subsequent studies have been more complex. In these series, perioperative mortality ranges from 14 to 24 percent[50–52] with a morbidity of 25 to 31 percent[51,52] and a paraplegia rate of 0 to 11 percent.[50,52] Moreover, Chiesa and colleagues[51] found that hybrid procedures had similar morbidity and mortality as traditional

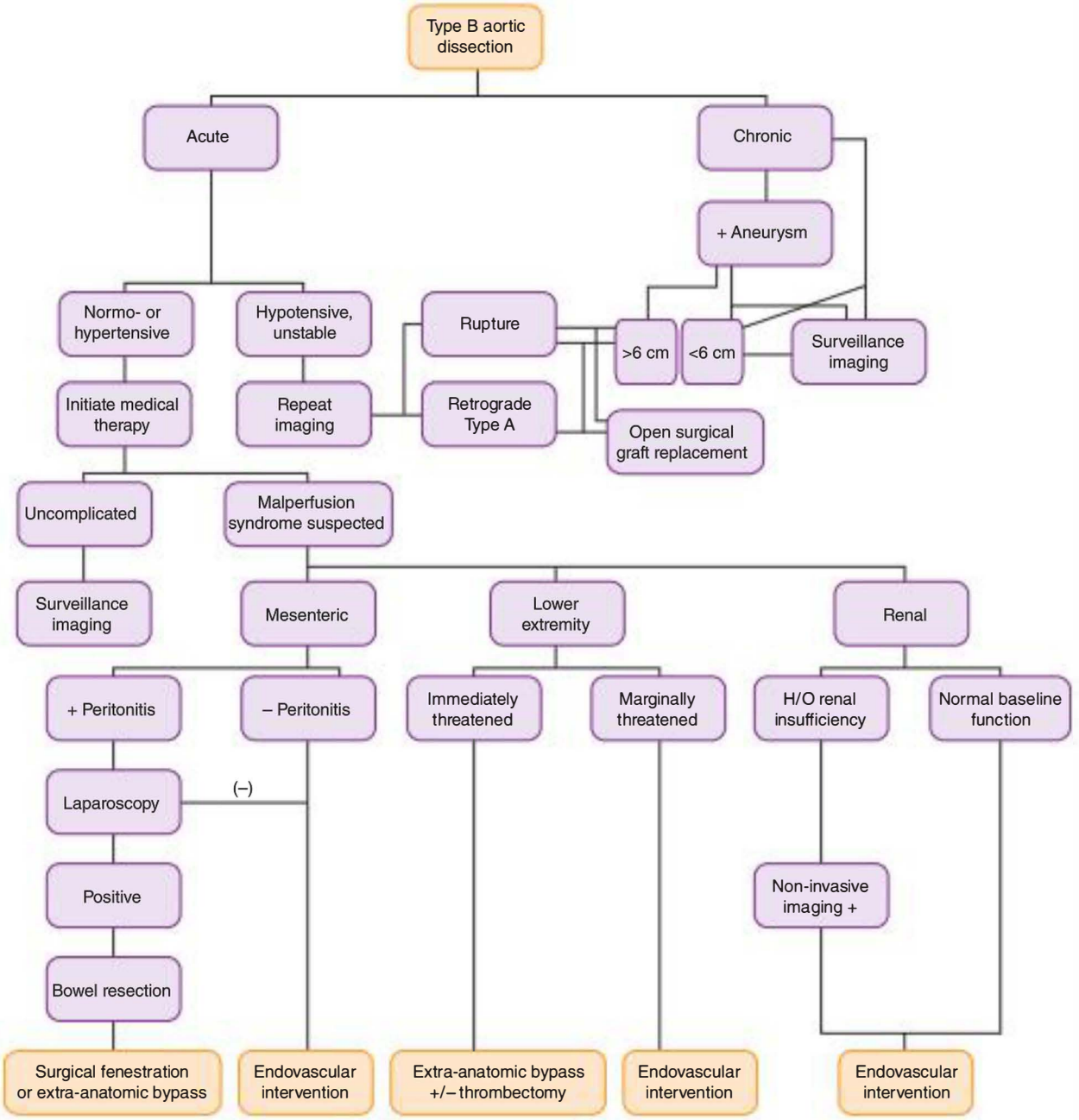



**FIGURE 42-6** The Johns Hopkins Hospital approach to aortic dissection.

open procedures, though their numbers were small. Of note, in most series, hybrid approaches were undertaken because the patients were thought to be too high risk for traditional TAA repair.

In summary, early results with hybrid approaches to TAAs are promising, and although subsequent studies have failed to demonstrate significant advantages, contemporary studies are small and underpowered to detect a difference. This problem is further complicated by the wide range of aneurysmal extent reported in these studies (Crawford I–IV) and wide variability in comorbidities and prior aortic surgery. Moreover, many questions including the timing of the staged operations (simultaneous vs delayed) remain to be elucidated. Large, multicenter, prospective data are needed to determine which patient population is most likely to benefit from this alternative therapy.

## PENETRATING ATHEROSCLEROTIC ULCERS AND INTRAMURAL HEMATOMAS

First described by Shennan in 1934, penetrating atherosclerotic ulcers (PAUs) were characterized fully by Stanson and colleagues in 1986.[53] IMHs were described earlier by Krukenberg in 1920.[54] Diagnostically, IMHs are confirmed by regional aortic wall thickening over 7 mm on CT scan or MRI in the absence of an intimal flap and without enhancement after contrast injection (Fig. 42-7).[55] Each of these entities presents much like aortic dissection, with sharp chest (ascending aorta) or back (descending aorta) pain.[56] In fact, among patients with acute aortic symptoms, 5 to 15 percent of cases are attributable to IMH.[57]

Cases of IMH with PAU tend to occur in the descending thoracic aorta (type B), whereas cases of IMH without PAU are grouped in the ascending aorta (type A). Ascending PAUs carry a 57 percent mortality while descending PAUs result in 5 percent mortality and 12 percent dissection.[57] Similarly, 28 percent of cases of type A IMH ended in aortic rupture, compared with only 9 percent of cases of type B IMH in the study by von Kodolitsch et al.[58] Moreover, 25 percent of cases of IMH without PAU progressed to dissection in the ascending aorta, whereas 13 percent did in the descending aorta. Thus, it has been suggested that type B IMH may be treated conservatively, whereas type A IMH warrants aggressive management.[55]

From the pathologic perspective, PAUs and IMHs seem to exist on a continuum: When a PAU gains intramural access of sufficient depth, the dissecting process commences, leaving a crescentic ring of blood in the aortic wall characteristic of IMHs. IMHs originate in severely diseased aortas that have been subject to severe hypertension. Unlike dissection, no intimal tear is visualized radiographically with IMHs. Nonetheless, a crescentic column of clotted blood fills the space that would be the false lumen in a typical dissection.[56]

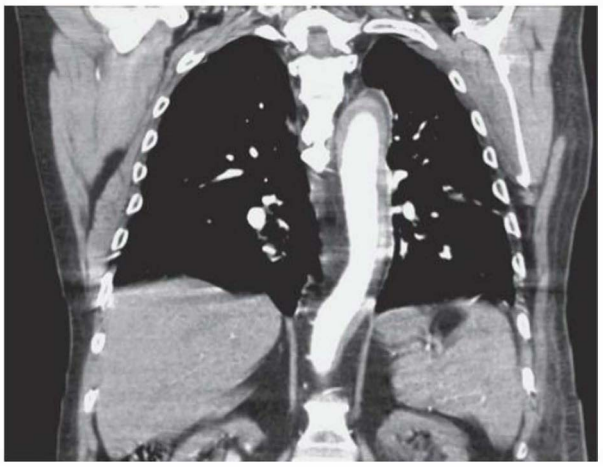


**FIGURE 42-7** Computed tomography, coronal view, of an intramural hematoma.

Explanations for the origin of this blood have ranged from the spontaneous rupture of the vasa vasorum, to the fracture of an atheromatous plaque, to disruption of a PAU that violates the internal elastic lamina, allowing transit of blood into the layers of the aortic wall.[59,60]

The natural history of IMHs has been reported to range from progression, to false aneurysm, to spontaneous regression, to dissection, and even to rupture.[55,56] A recent report correlated initial aortic diameter with progression to a catastrophic result from IMH; patients presenting with an initial aortic diameter greater than 40 mm had a 30-fold increased risk of progression to aneurysm formation or rupture. Furthermore, progression was nine fold more common in patients with an initial aortic wall thickness greater than 1 cm.[61] However, PAUs carry a more severe prognosis than do IMHs: Forty to fifty percent of acutely symptomatic patients progress to acute dissection or aortic rupture during the initial hospital admission.[62] Uncontrollable pain, increasing pleural effusion, and larger diameter and depth of PAU all portend progressive disease courses.[57] Therefore, early surgical intervention is recommended for symptomatic penetrating ulcers.[63]

Patients with PAU tend to be older and to have multiple comorbidities. Coady et al.[59] found a mean age of 77 years compared with 54 years for type A and 67 years for type B dissections ($p = 0.01$).[59] Associated comorbidities include hypertension,[53,55] COPD, and CAD.[21,57] Fully 40 percent of patients with PAU have been treated previously for AAA, a figure that indicates their extensive degenerative disease. Moreover, these patients carry a more severe prognosis than do those with dissection with a mortality rate of 40 vs 7.3 percent for type A and 4 percent for type B dissection.

Several studies have examined the outcomes of PAUs treated with TEVAR (Table 42-4).[64–66] Patel et al.[66] reported their experience with 37 patients in 2010. In this series, indications for intervention included rupture, symptoms, or the formation of a saccular aneurysm in an asymptomatic patient. Other patients were managed medically. Patients considered high risk for traditional open repair or who desired endovascular repair and had favorable anatomy

**TABLE 42-4: Results of Endovascular Repair of Penetrating Atherosclerotic Ulcers**

| | Schoder (2003) | Demers (2004) | Patel (2010) |
|---|---|---|---|
| Technical success | 100% | 100% | 100% |
| Mortality | 0% | 12% | 5.4% |
| Complication rate | 12.5% | 19% | 13.5% |
| Paraplegia | 12.5% | 0% | 0% |
| Endoleak | 12.5% | 8% | NR |
| Mean follow-up | 14.1 months | 51 ± 37 months | 32.6 ± 42.9 months |

NR, not reported.

were treated with TEVAR. All procedures were technically successful. In-hospital mortality was 5.4 percent, with both patients succumbing to ruptured aneurysms. No patients suffered permanent paraplegia. Actuarial freedom from TEVAR treatment failure was 81.6 percent at 5 years. On multivariate analysis, patients with IMH associated with their PAU were at higher risk of treatment failure. Thus, in this elderly and often debilitated patient population, TEVAR is a safe and effective treatment. Since patients with an associated IMH are at higher risk of treatment failure, careful assessment of the need for immediate versus delayed therapy is warranted.

## ENDOVASCULAR MANAGEMENT OF THORACIC AORTIC TRAUMA

Blunt aortic injury (BAI) secondary to trauma is a devastating injury. Over 85 percent of these patients die on the scene[67] and most who survive to the hospital suffer from multisystem injuries, rendering open surgical repair an unattractive option. Open surgical repair carries a mortality rate of 18 to 31 percent with a paraplegia rate of 2 to 14 percent[67,68]; however, without surgery, mortality can be as high as 55 percent.[67] Given the substantial morbidity and mortality associated with open repair of BAI, there is an increasing trend toward endovascular treatment of traumatic aortic injury. In fact, as of 2008, approximately 65 percent of BAI are treated endovascularly.[69]

The diagnosis of BAI was traditionally made with chest x-ray (CXR). Plain film criteria for aortic injury include loss of the aortopulmonary window, an abnormal aortic arch, a rightward tracheal shift, and a widened mediastinum.[67] However, 20 percent of patients with BAI have a normal CXR.[70] The long time gold standard for diagnosis was aortography (Fig. 42-8); however, in a landmark study, Fabian et al. demonstrated that helical CT scanning had a greater sensitivity for detecting BAI than did aortography (100 vs 92 percent).[70] Thus contemporary recommendations suggest helical CT for unrestrained patients involved in accidents at speeds greater than 10 mph and restrained patients in accidents greater than 30 mph.[67]




**FIGURE 42-8** Computed tomography, sagittal view, of a traumatic aortic transaction at the isthmus opposed to the left subclavian artery (LSA). LSA coverage anticipated. Narrow arches in young trauma patients present challenges to current devices.

Although immediate repair of BAI is recommended, it is often not possible secondary to multisystem injuries. Several studies have shown that delayed repair is safe if medical treatment with β-blockade and antihypertensive is undertaken. Fabian et al.[70] have demonstrated that while nonoperative management carries a high mortality rate, none of the patients in their series who were managed medically died from ruptured BAI. Other studies corroborate this finding, with an aortic-related mortality in patients managed medically of 4.8 percent.[71] In addition, in a large retrospective study, Estrera et al.[72] reported only 1 death (2 percent) from delayed repair. In fact, on multivariate analysis, delayed repair was protective against early mortality.

The results of endovascular treatment for traumatic aortic pathology are summarized in Table 42-5. The 2002 study by

**TABLE 42-5: Results of Endovascular Repair of Traumatic Aortic Injury**

| | Bartone (2002) | | Neschis (2009) |
|---|---|---|---|
| Traumatic pathology | Traumatic PSA–immediate | Traumatic PSA–delayed | Traumatic PSA, intimal tear, adventitial hematoma |
| Technical success | 100% | 100% | 100% |
| Mortality | 0% | 0% | 11.6% |
| Complication rate | 10% | 10% | NR |
| Paraplegia | 0% | 0% | 0% |
| Endoleak | 0% | 0% | 14.3% |
| Mean follow-up | 14.8 ± 7.8 months | 14.8 ± 7.8 months | 7.4 months |

PSA, pseudoaneurysm; NR, not reported.

Bortone et al.[41] included a subset of patients with traumatic aortic pseudoaneurysms. Those authors achieved 100 percent technical success with no deaths or paraplegia. There was 1 patient among 10 who required removal of his stent at 2 weeks secondary to compression of the left mainstem bronchus. As with thoracic aortic dissections, those authors advocated immediate endovascular repair rather than waiting more than 2 weeks: Delayed treatment is thought to be associated with the creation of fibrous and calcified connective tissue in the aortic wall, leading to further complications in treatment. In contrast, in the 6 patients (of 10) treated within 2 weeks of traumatic aortic pseudoaneurysm, aortic wall healing was seen in the 1-year follow-up CT scan.[41]

Neschis et al.[69] treated 43 consecutive patients from 2004 to 2008 with traumatic aortic injury with TEVAR. In their series, 13 patients needed exploratory laparotomy, 3 needed fracture fixation, and 1 needed a craniotomy resulting in an average aortic repair delay of 7 days. They reported a perioperative mortality of 11.6 percent, none related to endograft complications, and no permanent paraplegia. However, 14.3 percent of repairs were complicated by endoleaks and three of these patients eventually had open repair with endograft explantation. This study suggests that in patients with anatomically suitable lesions, endovascular intervention is the preferred treatment of BAI. This conclusion is supported by other studies demonstrating that TEVAR carries a lower rate of mortality than all types of open repair, included procedures involving clamp-and-sew, distal aortic perfusion, and cardiopulmonary bypass.[72]

Although a consensus is emerging that endovascular repair of BAI is the treatment of choice in anatomically acceptable candidates, with improved morbidity and mortality, the long-term durability of these devices remains unknown. This is a particularly important consideration as trauma patients with BAI tend to be much younger than the aneurysmal patients more commonly treated with these devices.

## COMPLICATIONS

The emergence of thoracic aortic stent grafting as the primary and often preferred treatment modality for many aortic pathologies has introduced a new spectrum of complications. Three areas merit special attention: spinal cord ischemic injury (SCI), retrograde dissection into the arch, and the consequences of left subclavian coverage.

SCI manifesting as paraplegia or paraparesis has been reported in several series, with an incidence of 0 to 12 percent.[73] The mechanism of the occurrence of SCI is not completely understood but may involve both primary spinal artery interruption by coverage by stent grafting and hypoperfusion caused by hypotension, which renders the collateral supply ineffective in spinal cord homeostasis. Evidence for this hypothesis stems from the open surgical literature and the elevated risk appreciated in patients undergoing thoracic endografting in whom prior AAA repair was performed (because lumbar arteries were oversewn).

A recent report by Cheisa et al.[74] examined perioperative risk factors to attempt to predict which patients would be at the highest risk for SCI. Over 5 years, 103 patients underwent endovascular repair of thoracic aortic disease ($N = 88$ TAA, $N = 10$ type B dissection, $N = 5$ PAU). CSF drainage was employed in seven patients on the basis of prior AAA repair or the need to cover T8 to L2 critical intercostals/lumbars. SCI was noted in four patients (4 percent), with all deficits occurring 24 to 96 h after the primary procedure. All deficits resolved with the institution of CSF drainage, steroids, and maintenance of MAP above 90 mm Hg. All patients with SCI were noted to have the lowest perioperative MAP below 70 mm Hg ($p < 0.001$). No other preoperative demographic or anatomic correlate of the procedure was significant on univariate analysis. In addition, other series have reported that the length of aorta covered with endografts is independently associated with the risk of spinal cord ischemia.[75] Accordingly, vigilance should be maintained in the perioperative period to avoid arrhythmias, anemia, and hypotension, particularly with intervention on a significant distance of the aorta, as spinal perfusion pressure may be marginal in the immediate perioperative period.[74]

Retrograde dissection (into the arch and ascending aorta) created by the mechanical force of the thoracic stent-graft interfacing with the proximal aorta has been described.[76] It is important to recognize that this may occur during, immediately after, or weeks after the primary thoracic stent-graft implantation. In a report by Eggebrecht and coworders,[77] there were 63 reported cases of retrograde ascending aortic dissection reported from the 28 centers participating in the European Registry on Endovascular Aortic Repair Complications, an incidence of 1.33 percent. Of these, 81 percent occurred in patients undergoing TEVAR for dissection. In this series, 42 percent were fatal. Most (64 percent) were discovered during follow-up, with 25 percent being asymptomatic and 19 percent presenting with sudden death. Although the association with dissection suggests that some cases of retrograde dissection result from a progression of the underlying disease, many likely result from procedure-related damage to the aortic wall either from the graft itself or from manipulation of guide wires and sheaths. Violation of the aortic wall creates the nidus that subsequently blossoms into a florid dissection. The variability in presentation, timing, and location underscores the need for regular surveillance of all patients who have been treated with the emerging technology of thoracic aortic endografting.

Coverage of the LSA for the purpose of extending the length of a proximal aortic seal has undergone a significant change in its treatment paradigm. Theoretical concerns about left upper extremity ischemia are not commonly encountered clinically. However, collateral supply to the spinal cord may derive from the thyrocervical trunk, which is dependent on LSA perfusion. Therefore, coverage of the LSA can be associated with rare but devastating neurological sequelae. Although a recent series of 171 patients demonstrated an absence of true malperfusion syndrome,[78] several centers are routinely revascularizing covered LSAs

prophylactically[79] In a landmark trial of over 600 TEVAR patients, there was an 8.4 percent incidence of paraplegia or stroke in patients who had LSA coverage versus a 0 percent incidence in those who underwent prophylactic revascularization.[80] These potential neurological sequelae have led some to rethink their approach to LSA coverage. Many have suggested definition of the head and neck arterial anatomy with CTA, recommending consideration of elective revascularization for the following indications: small right subclavian artery; patent left internal mammary coronary artery bypass; patent left axillary–femoral bypass; functional left arm arteriovenous fistula; patient left-handedness; aberrant aortic arch anatomy; or extensive thoracic aortic coverage with a history of prior abdominal aortic procedures.[81,82]

## SUMMARY

Stent-graft therapy of the full spectrum of thoracic aortic pathologies is a rapidly developing and emerging technology. On the basis of satisfactory early and midterm results combined with the obvious avoidance of major cavitary incisions and recovery thereafter, thoracic aortic stent grafting has assumed a role as a primary therapy for aneurysms, dissections, penetrating aortic ulcers, and traumatic lesions. Not only have endovascular surgeons recognized the advantages of thoracic stent grafts, patients are demanding consideration for such "minimally invasive" options. Open thoracic aortic surgery may become reserved for cases in which anatomy and topography prohibit safe graft implantation. Surgeons who want to apply this technology to benefit their patients must conduct appropriate preoperative planning and imaging, have a solid base of fundamental skill with catheter-based interventions, and recognize the need for regular, lifelong surveillance of all patients treated with thoracic aortic endografts.

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## ENDOVASCULAR REPAIR OF THORACIC AORTIC PATHOLOGY BOARD REVIEW QUESTIONS (CHAPTER 42)

1. Which of the following is the optimal study for evaluation of blunt aortic injury?
   A. Plain radiography
   B. Aortography
   C. Computed tomography
   D. Transthoracic echocardiography
   E. Serum biomarkers

2. Which of the following is correct regarding endoleak?
   A. Type I = poor seal between the graft and the proximal aorta
   B. Type II = poor seal between the graft and the distal aorta
   C. Type III = blood leakage through the graft material
   D. Type IV = back bleeding from branch vessels
   E. Endoleak occurs in less than 10 percent of patients.

3. Which of the following is not associated with increased risk of spinal cord ischemia during endovascular thoracic interventions?
   A. Prior aortic surgery
   B. Hemodynamic instability
   C. Length of aortic coverage
   D. Cerebrospinal fluid drainage
   E. Left subclavian coverage

4. Which of the following is true regarding endovascular repair of descending thoracic aortic aneurysm?
   A. The cost is equivalent to open repair.
   B. Mortality is higher than open repair.
   C. There has not been evaluation for the treatment of ruptured aneurysm.
   D. Only one device is FDA-approved for treatment of aortic aneurysm.
   E. Technical success is variable.

5. Which of the following is not a potential indication for prophylactic left subclavian artery revascularization prior to left subclavian artery coverage with a thoracic endograft?
   A. Patent left internal mammary artery to left anterior descending artery graft
   B. Absent or atretic right vertebral artery
   C. Patent left arm arteriovenous dialysis shunt
   D. Heavily calcified or stenotic left subclavian artery origin
   E. History of prior abdominal aortic procedures

## ANSWERS

1. **Answer: C.** Computed tomography (CT) is the best study to evaluate blunt aortic injury, as it is highly sensitive, noninvasive, and rapid. Plain chest radiographs will be normal in 20 percent of patients with blunt aortic injury. Aortography is less sensitive and more invasive than CT. TTE is less sensitive and specific than CT and is unable to image the aortic arch.

2. **Answer: A.** A type I endoleak occurs when there is inadequate seal between the graft and the distal or proximal aorta. A type II endoleak occurs when there is back bleeding from branch vessels. A type III endoleak occurs when there is blood excursion between graft components. A type IV endoleak occurs when there is blood leakage through the graft material. Endoleak is common, occurring in 13 to 30 percent of patients.

3. **Answer: D.** In several randomized trials, cerebrospinal fluid has been associated with a decreased risk of spinal cord ischemia. Prior infrarenal abdominal aortic aneurysm repair, hemodynamic instability, increasing length of endograft aortic coverage, and left subclavian coverage have all been associated with increased risk of spinal cord ischemia.

4. **Answer: A.** Endovascular repair of descending thoracic aortic aneurysm has a similar cost to open repair, as the high cost of the devices offset the shorter hospitalization. TEVAR has a similar mortality to open repair and has been shown to effective and safe for the treatment of ruptured aneurysms. There are currently three FDA-approved devices, all of which have high technical success rates.

5. **Answer: D.** A heavily calcified or stenotic left subclavian artery origin will likely not require prophylactic left subclavian artery revascularization. The remaining conditions can potentially result in compromised flow to the heart (left internal mammary artery graft), the brain (absent/atretic right vertebral artery), access (left arm dialysis shunt), or the spinal cord (prior abdominal aortic procedures) after occlusion of the left subclavian artery with an endograft.

# 43

# Surgical Therapies for Atrial Fibrillation

*Timo Weimar*
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**KEY CONCEPTS**

- Epidemiology
  - Atrial fibrillation (AF) affects about 2 percent of the general population. It is strongly correlated to age and the prevalence increases to 10 to 15 percent in patients over the age of 80. It is associated with hypertension, heart failure, valvular heart disease, and ischemic heart disease. In 10 to 15 percent there is no underlying cardiac pathology present (lone AF).
- Pathophysiology
  - AF requires both an initiating event and a permissive atrial substrate. While automaticity and triggered activation is often, but not exclusively, found within and around the pulmonary veins and is involved in AF initiation, different mechanisms of reentry in both atria also play an important role in sustaining AF. As the atrial size increases, the conduction velocity slows or the atrial refractory period decreases, and the probability of initiating and sustaining AF increases.
- Clinical features
  - Besides symptoms, hemodynamic compromise, and tachycardia-induced cardiomyopathy, stroke remains the most feared complication. AF accounts for about 25 percent of strokes in patients older than 80 years and increases a person's risk of stroke by 5-fold.
- Diagnostics
  - A transthoracic and transesophageal echocardiogram should determine left atrial diameter and evaluate for the presence of a left atrial thrombus. A cardiac catheterization will provide information about the presence of coronary artery disease and the anatomical location of the circumflex coronary artery. In patients who have failed catheter ablation, chest computerized tomography (CT) is indicated to assess for pulmonary vein stenosis.
- Treatment
  - The surgical procedures currently performed to ablate AF include the biatrial Cox-Maze procedure (CMP), left atrial lesion sets, and pulmonary vein isolation. All of these operations have been simplified by alternative energy sources.
- Outcome
  - Success rates vary and depend on the lesion set performed, the energy source used, the type of AF, and the presence of concomitant pathology. The biatrial CMP has an approximately 90 percent success rate for all types of AF and has set the benchmark for alternative lesion sets as well as for new and less invasive approaches currently under development.

## INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide with an increasing incidence with age. Adults at the age of 40 years have a 25 percent risk of developing AF during their lives.[1] The actual incidence and prevalence of AF is likely underestimated due to undetected asymptomatic occurrences or patients ignoring paroxysmal episodes. Experts predict that the number of AF-related hospitalizations will increase and almost double to 3.5 million by the year 2025 in the United States.

Although AF itself is not considered a life-threatening arrhythmia, it is associated with significant morbidity and mortality secondary to hemodynamic compromise and tachycardia-induced cardiomyopathy in some patients. Besides palpitations resulting in discomfort and anxiety, the loss of synchronous atrioventricular contractility may cause various degrees of ventricular dysfunction, exercise

intolerance or congestive heart failure in patients with AF. Furthermore, stasis of blood flow in the fibrillating left atrium increases the risk of thrombus formation. Thromboembolic events and stroke remain the most feared complication in these patients. AF accounts for about 25 percent of strokes in patients older than 80 years and increases a person's risk of stroke by 5-fold.[2] Overall, AF has been identified as an independent risk factor for mortality. Using the data from the Framingham study, the established risk factor–adjusted odds-ratio for death in men and women with AF was 1.5 and 1.9, respectively.[3]

The pharmacological treatment of AF has been disappointing with failure rates as high as 60 percent. Besides the significant side effects associated with antiarrhythmic drugs, their long-term efficacy in maintaining normal sinus rhythm is poor. In the AFFIRM-trial, rhythm control strategies were compared to rate control and anticoagulation. There was no survival benefit of rhythm over rate control. This appeared to be due to the use of antiarrhythmic drugs to maintain sinus rhythm as the AFFIRM-trial confirmed that the presence of normal sinus rhythm significantly decreased the risk of death with a hazard ratio of 0.53 ($p$ <0.001).[4]

The persistent limitations of pharmacological therapy of AF have led to the development and proliferation of interventional approaches in the treatment of AF over the past two decades. The most promising and successful options have included catheter ablation and surgery. Strategies for interventional treatment have been based on the type of AF. A recent consensus statement of the Heart Rhythm Society, the European Heart Rhythm Association, the American College of Cardiology, the American Heart Association, and the Society of Thoracic Surgery defined three different types of AF including paroxysmal, persistent, and longstanding persistent AF (Table 43-1).[5] The foundation of catheter ablation has been the isolation of the pulmonary veins (PVI). Results have been variable with single-procedure success rates between 16 and 84 percent.[5] Although PVI has had good success rates in most patients with paroxysmal AF, certain patient subgroups have done poorly, such as patients with longstanding persistent AF and large atria. A recent report from Haïssaguerre's group, who pioneered PVI, reported a single procedure success rate as low as 29 percent after 5 years.[6] The surgical treatment of AF has had higher success rates in preventing AF recurrence. The biatrial Cox-Maze procedure (CMP) III has been the gold standard for more than one decade, with a freedom from symptomatic AF of 97 percent, and has been equally effective in all types of AF.

**TABLE 43-1: Definition of Atrial Fibrillation**

*Paroxysmal AF* is defined as recurrent AF (≥2 episodes) that terminates spontaneously within 7 days

*Persistent AF* is defined as AF that is sustained beyond 7 days or lasting less than 7 days but necessitates pharmacological or electrical cardioversion

*Longstanding persistent AF* is defined as continuous AF of greater than 1-year duration

The term *permanent AF* refers to a patient group where a decision has been made not to pursue restoration of sinus rhythm by any means, including catheter or surgical ablation

## PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

AF is a manifestation of a complex and progressive disease of the atria with electrical, contractile and structural remodeling that, in most incidences, gradually worsens over time.[7]

There are four main components that play an important role in the initiation and sustention of AF: (1) a trigger, which can be a single premature or a run of focal ectopic depolarization; (2) the effective atrial refractory period; (3) the conduction velocity; and (4) the geometry or anatomy of the atrium. Although the precise mechanisms that cause AF are incompletely understood, AF appears to require both an initiating event and a permissive atrial substrate. There is supportive data for multiple wavelets, mother waves, fixed or moving rotors, and macro-reentrant circuits playing a role in AF, and in a given patient, multiple mechanisms may coexist at any given time.

### Automaticity and Triggered Activity

Enhanced automaticity occurs when myocytes possessing pacemaker activity increase their rate of spontaneous discharge. It can be due to a lowered threshold of the action potential upstroke, a less negative maximal diastolic potential, or an increase in the slope of spontaneous diastolic depolarization. Triggered activity arises from membrane oscillations following normal action potentials. If such oscillation reaches threshold of depolarizing currents, they can provoke new action potentials. Under certain circumstances, such triggered responses can in turn elicit new action potentials, resulting in self-sustaining runs of triggered activity. After Haïssaguerre and colleagues reported on the role of pulmonary veins (PVs) in initiating AF, most interventional treatment strategies focused on the isolation of triggers from these anatomic sources.[8] While paroxysmal AF often initiates in the PVs, biatrial mapping studies have shown that the premature beats that trigger AF were located in the PVs in only 53 percent of the time. However, data about the presence of pacemaker cells in the PVs or other atrial areas outside the sinus node are controversial. The conduction velocity within the PVs is slower (0.3 m/s) compared with the surrounding atrial tissue (0.9 m/s). The complex fiber orientation spiraling perpendicularly around the vein with other fibers running parallel to the vein, and the lack of Connexin 40 in the veins, a major determinant of conduction velocity in the atria, probably contribute to this slower conduction. This creates heterogeneity of electrical conduction around the PVs, which is theorized to promote reentry and sustained

AF. Although the PVs have the substrates needed to initiate and maintain AF in some patients, in almost 50 percent of cases there are sources present outside the PVs. In the group of patients undergoing concomitant cardiac surgery for structural heart disease, it is important to remember that the underlying mechanisms cannot be necessarily translated from experiences drawn from the electrophysiological laboratory with lone AF.

## Mechanisms of Reentry

There are multiple theories for the development of reentrant circuits in the atrium.[9] *Circus movement reentry* is characterized by an activation that can travel around a preformed anatomical structure, like the orifice of the PVs, and reactivate previously excited tissue. A short refractory period and a low conduction velocity make circus movement reentry more likely. The minimal path length for circus movement reentry can be calculated as the product of conduction velocity and refractory period (wavelength). If the path of the circuit is longer than the wavelength, there is a delay between recovery of the tissue and the moment of reexcitation, which is called the "excitable gap" (Fig. 43-1A). Initiation of *circus movement reentry* requires unidirectional conduction block often occurring in regions with long refractory periods.

In the *leading circle concept*, the reentrant circuit does not require an anatomical obstacle but rather moves around a core that is not fully activated. The dynamics of reentry are determined by the smallest possible loop in which the impulse can continue to circulate. Under this condition, the wavefront must propagate through relatively refractory tissue, making it a relatively unstable reentrant since there is no fully excitable gap (Fig. 43-1B). In the *spiral wave theory*, the rotor rotates around an unexcited yet excitable core. Along the wavefront, there is a decline in conduction velocity until block occurs (dotted line in Fig. 43-1C). One way of visualizing such a wave is to think of a broken wave that curls at its broken end and begins to rotate. Multiple unstable rotors resemble conduction patterns similar to that of the *multiple wavelet hypothesis*. According to Moe's computer simulation, wavefronts continuously undergo wavefront–wavetail interactions resulting in wave breaks and generation of new wavefronts (Fig. 43-1D).

As the underlying distribution of refractory periods becomes more heterogeneous, unidirectional block can occur. This is a necessary condition for the initiation of reentry. When unidirectional block occurs, reentrant arrhythmia will initiate only if a critical mass of tissue is present. The critical mass is determined by the wavelength of the reentrant circuit. As atrial size increases, conduction velocity is slowed or the atrial refractory period is decreased, and the probability of initiating and sustaining AF increases. Although numerous non-pharmacologic approaches to treat AF, like isolating triggers in PVs, have involved altering one of these substrates, it must be remembered that the other substrates can still be active.

## Atrial Remodeling

Studies of Alessie in the early 1990s advanced our understanding of AF by the observation that AF itself induces changes in the atrium that result in an increased susceptibility to further AF.[10] He demonstrated that, during atrial pacing, action potential duration and atrial refractory period both decreased. This electrical remodeling led to sustained AF. However, structural changes of the atrium contribute to this remodeling process as well. Age, hypertension, congestive heart failure, or heart valve diseases are all strong predictors for the development of AF. These characteristics all increase atrial wall stress and some degree of dilatation in the atria by increased volume or pressure load. All these conditions can be the cause of the development of fibrosis and myocyte hypertrophy. These pathological changes can result in slow conduction or conduction block in some areas of the atrium, further increasing susceptibility to AF.

# EPIDEMIOLOGY

AF affects about 2 percent of the general population and almost 3 million people in the United States. It is strongly correlated to age and the prevalence increases from 0.1 percent in persons younger than 55 years to about 5 percent in persons 60 years or older and approaches 10 to 15 percent for patients over the age of 80. Overall, significantly more men than women are affected by AF.

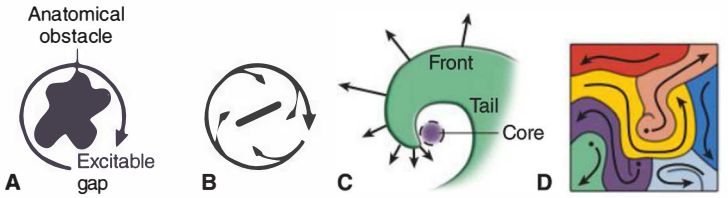



**FIGURE 43-1** Mechanism of reentry: **A.** Circus movement reentry. **B.** Leading circle concept. **C.** Rotor theory reentrant. **D.** Multiple wavelet hypothesis. (Reproduced with permission from Schotten U, et al. Pathophysiological mechanisms of atrial fibrillation: A translational appraisal. *Physiol Rev* 2011;91:265–325.)

There are a number of cardiovascular disorders associated with AF including hypertension, heart failure, valvular heart disease, and ischemic heart disease. All of these comorbidities can cause increased stress on the atrial wall resulting in interstitial fibrosis and atrial dilatation. However, in 10 to 15 percent of patients, there is no underlying cardiac pathology present (lone AF).

Stasis of atrial blood and resultant thrombus formation associated with AF increases a person's risk of stroke by 5-fold and the rate of stroke averages about 5 percent/year in affected patients. It increases substantially in the presence of other cardiovascular diseases. While the prevalence of stroke is low in patients under the age of 60 at less than 0.5 percent, it approaches 30 percent for patients between 80 and 90 years. The intensity of anticoagulation involves a balance between prevention of ischemic stroke and avoidance of hemorrhagic complications. An international normalized ratio (INR) of 2 to 3 is recommended in patients with AF.

AF is a costly public health issue. A study analyzing three federally funded databases in the United States in 2005 suggested a total annual cost of US$6.65 billion for the treatment of AF, including US$2.93 billion (44 percent) for hospitalizations with a principal discharge diagnosis of AF, US$1.95 billion (29 percent) for the incremental inpatient cost of AF as a comorbid diagnosis, US$1.53 billion (23 percent) for outpatient treatment of AF, and US$235 million (4 percent) for prescription drugs.[11] In all analyses, AF was a significant contributor to hospital cost.

## INDICATIONS FOR SURGICAL ABLATION

The indications for surgical ablation have been defined in a recent consensus statement and include[5]:

1. All symptomatic patients with documented AF undergoing other cardiac surgical procedures
2. Selected asymptomatic patients with AF undergoing cardiac surgery in which the ablation can be performed with minimal risk in experienced centers
3. Stand-alone surgery should be considered for symptomatic patients with AF who either prefer a surgical approach, have failed one or more attempts of catheter ablation, or are not candidates for catheter ablation.

There is still controversy regarding the referral of patients for surgery with medically refractory, symptomatic lone AF in lieu of less invasive catheter ablation. In our opinion, there are relative indications for surgery that were not included or expressed in the consensus statement:

1. AF patients who develop a contraindication to long-term anticoagulation and have a high risk for stroke (CHADS score ≥2) are excellent candidates for surgery. The CMP not only is able to eliminate AF in most of these patients, but also amputates the left atrial appendage, which is known to be one of the main sources of atrial thrombus formation. The stroke rate following the procedure off anticoagulation has been remarkably low, even in patients with high CHADS scores.
2. Patients with longstanding AF who have suffered a cerebrovascular accident despite adequate anticoagulation are at high risk for repeat neurological events. In our experience of over 200 patients with a stand-alone CMP, there was only one late stroke, with over 80 percent of patients off anticoagulation at last follow-up. This is remarkable in that about 20 percent of patients had experienced at least one cerebrovascular accident before surgery.
3. AF patients with a clot in the left atrial appendage are not candidates for catheter ablation and should be considered for surgical ablation.

In the era of minimally invasive approaches, including thoracoscopic and hybrid procedures, a team approach including both electrophysiologists and surgeons should be established to ensure appropriate patient and treatment selection.

## ELECTROPHYSIOLOGICAL EVALUATION AND DIAGNOSTIC MODALITIES

It has not been possible to locate the precise mechanism of AF in the majority of patients prior to surgery due to the limitations of endocardial non-contact mapping and the invasiveness of epicardial mapping. Traditional epicardial activation sequence mapping is difficult and time-consuming and has not been suitable to provide useful real-time information during the procedure. Improvements in technology and further experimentation may provide the means for faster data analysis; a map-directed approach may be feasible in the future. Electrocardiographic imaging (ECGI) can be used to compute epicardial potentials noninvasively and reconstruct a 3-dimensional anatomical map of atrial electrical activity using multiple surface electrodes and anatomic data obtained through CT.

Besides documentation of the patient's heart rhythm prior to surgery, a preoperative transthoracic and an intraoperative transesophageal echocardiogram should be performed to determine the left atrial diameter and to evaluate for the presence of a left atrial thrombus. Left atrial size is a significant predictor of failure in our series and is important to define prior to surgery.[12] It is our policy that in patients with a left atrial size ≥7 cm, a left atrial reduction procedure should be considered. A cardiac catheterization will provide information about the presence of coronary artery disease. Moreover, the anatomical location of the circumflex coronary artery is important to define in order to safely perform the left atrial isthmus lesion and the ablation of the coronary sinus. In patients who have failed catheter ablation, a chest CT is indicated to assess for PV stenosis. It is also important to determine the precise atrial tachyarrhythmia in patients who have failed catheter ablation; that may require an electrophysiological study. Atrial tachycardia is usually not

amenable to surgical ablation and atypical atrial flutter usually necessitates a full Cox-Maze lesion set.

## DEVELOPMENT OF THE COX-MAZE PROCEDURE

In 1987, Dr. James Cox introduced the Maze procedure for the surgical treatment of AF at Washington University in Saint Louis. Following extensive experimental investigation, his surgical approach was designed to block the multiple macroreentrant circuits which were believed to be the cause of AF.[13] Unlike other historical attempts to address AF, such as the left atrial isolation procedure, His bundle ablation, the corridor procedure, or the atrial transection procedure, the CMP successfully restored both AV synchrony and sinus rhythm, thus potentially reducing the risk of thromboembolism and stroke. The operation consisted of creating surgical incisions in both the right and left atria. These incisions were placed in a pattern that allowed the propagation of the sinoatrial node impulse throughout both atria (Fig. 43-2A). This resulted in a preserved activation of most of the atrial myocardium, resulting in preservation of atrial transport function in most patients.

The original version, the *CMP I*, was modified due to problems with late chronotropic incompetence and a high incidence of pacemaker implantations. The *CMP II* was technically difficult to perform and was soon replaced by the final iteration known as the *CMP III* (Fig. 43-2B).[14] The CMP III, often referred to as the "cut-and-sew" Maze, became the gold standard for the surgical treatment of AF with excellent long-term success rates and a low postoperative risk of stroke.[15] In our series at Washington University, 97 percent of 198 consecutive patients who underwent this procedure with a mean follow-up of 5.4 years were free from symptomatic AF. There was no difference in success rates between patients undergoing a stand-alone CMP and those undergoing concomitant procedures and it was also equally efficacious in paroxysmal and persistent or longstanding persistent AF.[15]

Despite its proven efficacy, the CMP III was technically challenging and invasive, and few cardiac surgeons still perform this operation today. At most centers, the surgical incisions have been replaced with linear lines of ablation using a variety of different energy sources. These ablation-assisted procedures have greatly expanded the field of AF surgery in the last decade. With present ablation technology, surgery can be performed with low mortality and limited access incisions while preserving the high success rates of the traditional procedure.

In our laboratory, bipolar radiofrequency (RF) energy was found to be able to create reliable transmural lines of ablation on the beating heart in seconds while minimizing the risk of collateral damage to the surrounding tissue.[16,17] Since the energy is applied within the jaws of a clamp, it is inherently safer than unipolar sources.[18] It has been used successfully to replace most of the surgical incisions of the CMP III procedure. In 2002, the authors' group introduced an ablation-assisted procedure, termed the CMP IV, which has now been performed in almost 400 patients.

## SURGICAL ABLATION TECHNOLOGIES

The development of alternative energy sources to create transmural lines of ablation has revolutionized the field of antiarrhythmic surgery, making the procedures less time-consuming, easier to perform, and amenable to minimally-invasive approaches.

Several important criteria must be met by the chosen ablation technology to be considered as a replacement of surgical incisions: It must reliably produce bidirectional conduction block since this is the mechanism by which incisions either block macro- and microreentrant circuits or isolate trigger foci. Our laboratory has shown that this requires a completely transmural lesion, as even small gaps as narrow as 1.5 mm within ablation lines can conduct fibrillatory impulses. The second crucial characteristic of an ablation device is its safety. This requires a precise definition of dose–response curves to

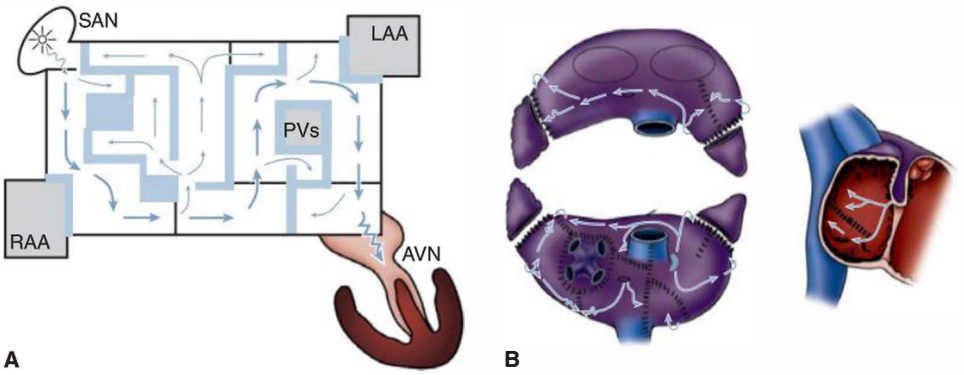



**FIGURE 43-2** **A.** Propagation of the sinus impulse throughout both atria in the original Cox-Maze procedure. **B.** The original cut-and-sew Cox-Maze procedure III. (Reproduced with permission from Cox JL, et al. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. *J Thorac Cardiovasc Surg* 1991;101:569–583. Copyright Mosby.)

limit excessive or inadequate ablation. The surgeon must also have knowledge of the effects of the specific ablation technology on surrounding vital cardiac structures, such as the coronary sinus, coronary arteries, valvular structures, such that the risk of collateral damage to surrounding extracardiac structures, like the esophagus or the phrenic nerve, is minimized. Third, a device should make AF surgery simpler, require less time to perform, and allow for a minimally invasive or endoscopic approach. This would require features such as rapidity of lesion formation, simplicity of use, adequate length and flexibility, and the ability to reliably create transmural lesions epicardially on the beating heart. Currently, no device has perfectly met all of these criteria.

It is necessary to understand the variability of human atrial wall thickness to define the performance of any epicardial ablation device. In normal individuals, the mean atrial thickness of the posterior left atrium (LA) between the PVs ranges from 2.3 ± 1.0 mm between the superior veins to 2.9 ± 1.3 mm between the inferior veins. In patients with a history of AF, the tissue is thinner, ranging from 2.1 ± 0.9 mm to 2.5 ± 1.3 mm. In both groups, the thickness increases, moving from the superior to the inferior veins. In normal individuals, the thickness in the LA just above the coronary sinus is 6.5 ± 2.5 mm. The thickness of Bachmann's bundle, a preferential conduction pathway between the right and left atria crossing across the roof of the atria in the transverse sinus, is 4.6 ± 1.1 mm (range: 1.7–9.3 mm) in normal individuals.

In patients with structural heart disease, reflecting more closely those patients referred for surgical ablation, the mean LA thickness is 5.2 ± 1.8 mm (range: 3–15 mm). The crista terminalis in the RA has an average thickness of 7.7 ± 2.4 mm (range: 4.2–12.6 mm). This has to be considered when comparing these patients to those treated by electrophysiologists in the catheterization laboratory without concomitant cardiac pathology. This wide range of wall thickness does not take into account overlying fat or underlying free running pectinate muscles. Even in normal individuals, the fat layer at the posterior mitral annulus can be 10 mm thick. Epicardial fat is a barrier to depth of penetration for most ablation technologies. In addition, there are free-running pectinate muscles in both the right and left atria that are not continuous with the epicardial surface. As patients grow older, their chamber size and wall thickness increase. This highly variable wall thickness and anatomy provide a challenge to any unidirectional device attempting to achieve transmural lesions.

The following sections will briefly summarize the current ablation "…technologies, including their advantages and disadvantages.

## Cryoablation

Cryoablation has been used to ablate arrhythmias for over 3 decades and has the benefit of preserving fibrous tissue and collagen. Because of this, it has been one of the safest energy sources available. As opposed to other alternative energy sources, cryoablation creates direct physical injury, a cumulative sublethal cellular stress response, and molecular-based cell death by freezing instead of heating. The formation of intracellular and extracellular ice crystals disrupts the cell membrane and causes cell death. A homogenous surface contact is essential for good ablation performance. Any fluid or vapor trapped between the probe and the targeted tissue freezes to form ice balls. Ice has a low thermal conductivity coefficient and increases thermal resistance. Thus, ice ball formation within the valleys of a nonuniform surface acts as an insulator, retarding heat loss. The onset of ice formation at the cryoprobe provides cryo-adhesion to maintain and ensure tissue contact and creates an area at which heat is extracted from the tissue. As heat is removed by various cryogens such as nitrous oxide or argon, extracellular fluid freezes at −20°C, creating a hyperosmotic environment that causes cell shrinkage and ultimately cell death.[19] Rapid freezing to −40°C induces expansion of intracellular ice formation that disrupts organelles and cell membranes even before osmotic imbalance occurs. A fast rate of cooling will increase cell death, while slowly thawing the tissue is also effective in prolonging the mechanisms of cell destruction.[19] Currently, two commercially available sources of cryothermal energy are being used in cardiac surgery. One is manufactured by AtriCure (Cincinnati, OH) and uses a disposable malleable linear probe or reusable rigid probes with nitrous oxide as the cooling agent. More recently, Medtronic (Minneapolis, MN) has distributed a malleable linear probe and a clamp device based on argon. At 1 atm of pressure, nitrous oxide is capable of cooling tissue to −89.5°C, while argon can reach a temperature of −185.7°C. Cryoablation has a well-defined efficacy and safety profile and is generally safe except around the coronary arteries. The relatively long time period of 1 to 3 min required to reliably create transmural lesions is one potential disadvantage of cryoablation. There is also difficulty in creating lesions on the beating heart due to the "heat sink" of the circulating blood. Furthermore, if blood is frozen during epicardial ablation on the beating heart, it coagulates, creating a potential thromboembolic risk.

## Radiofrequency Energy

RF energy has been used for cardiac ablation for many years in the electrophysiology laboratory, and was one of the first energy sources to be applied in the operating room. RF energy uses alternating current in the range of 100 to 1000 kilohertz (kHz). This frequency is high enough to prevent rapid myocardial depolarization and the induction of ventricular fibrillation, yet low enough to prevent tissue vaporization and perforation. The lesion size created by thermal injury depends on electrode–tissue contact area, the interface temperature, the current and voltage (power), as well as the duration of delivery. On histologic evaluation of radiofrequency lesions, a focal coagulation necrosis predominates acutely. This correlates with the irreversible nature of the injury, which occurs at temperatures greater than 50°C.

There is destruction of the myocardial collagen matrix and replacement with fibrin and collagen in chronic studies. At very high temperatures greater than 100°C, char formation predominates. Char is an impediment to heat transduction and has been associated with asymmetrical ablations. The depth of the lesion can be limited by char formation, epicardial fat, myocardial and endocavity blood flow, and tissue thickness. Resistive RF energy can be delivered by either *unipolar* or *bipolar* electrodes.

Numerous *unipolar RF* devices are currently on the market with popular devices distributed by Estech (San Ramon, CA), nContact (Raleigh, NC), and Medtronic (Minneapolis, MN). These include both dry and irrigated devices as well as devices which incorporate suction in an attempt to improve tissue surface contact. Resistive heating occurs only within a narrow rim of tissue in direct contact with the electrode, usually less than 1 mm. The deeper tissue heating occurs via passive conduction. To prevent char formation at the tissue–electrode interface, irrigated catheters were developed to keep temperatures cooler at the tissue interface. These irrigated catheters have been shown to create larger volume lesions than dry RF devices. While in animals, unipolar RF has been shown to create transmural lesions on the arrested heart with sufficiently long ablation times of 60 to 120 s; this has been more difficult in humans. After 2-minute endocardial ablations during mitral valve surgery, only 20 percent of the in vivo lesions were transmural. Epicardial ablation has been even more difficult. Animal studies have consistently shown that unipolar RF is incapable of creating epicardial transmural lesions on the beating heart. A recent clinical study confirmed this problem. Epicardial RF ablation in humans resulted in only 7 percent of lesions being transmural despite electrode temperatures of up to 90°C, which has been felt to be caused by the heat sink.[20] The complications of unipolar RF devices have been described after extensive clinical use and include coronary artery injuries, cerebrovascular accidents, and the devastating creation of esophageal perforation leading to atrial–esophageal fistula.

*Bipolar RF* technology is incorporated into devices in two ways. In one, the electrodes are embedded in the jaws of a clamp to focus the delivery of energy. Shielding the electrodes from the circulating blood pool, allows for faster ablation times and limits collateral injury to surrounding structures. The second way it is used is in a linear device in which the two electrodes are side-by-side and the device is applied to either the epicardial or endocardial surface. Bipolar RF ablation clamps are the most reliable devices for creating transmural lesions on the beating heart both in animals and in humans with short ablation times.[16,21,22] The linear pens developed for epicardial ablation on the beating heart have not been as reliable and, in a study from our laboratory, were not successful at creating linear lines of block in experimental models. Three companies (AtriCure, West Chester, OH; Medtronic, Minneapolis, MN; and Estech, San Ramon, CA) currently market bipolar RF devices. Use of the bipolar RF clamp devices have eliminated most of the collateral damage that occurred with the unipolar devices. This is likely due to the focused delivery of energy within the jaws of the clamp, eliminating the diffuse radiation of heat. However, the devices with side-by-side bipolar electrodes have not been extensively evaluated for safety yet and would have the same potential problems as unipolar devices.

## High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) is another modality being applied clinically for surgical ablation (St. Jude Medical, St. Paul, MN). Ultrasound effectively ablates tissue via mechanical hyperthermia. When ultrasound waves are emitted from the transducer, the resulting wave travels through the tissue causing compression, refraction, and particle movement. This translates into kinetic energy and ultimately thermal coagulative tissue necrosis. HIFU produces rapid, high-concentration energy in a focused area, and is reportedly able to create transmural epicardial lesions through epicardial fat in a short time.[23]

HIFU is unique in that it is able to create noninvasive, noncontact focal ablation in 3-dimensional volume without affecting intervening and surrounding tissue. It utilizes ultrasound beams in the frequency range of 1 to 5 megahertz (MHz) or higher, creating focused lesions quickly by rapidly raising the temperature of the targeted tissue to above 80°C, effectively causing cell death. By focusing ultrasound waves, HIFU is able to create targeted thermal coagulation of tissue at a very well-defined focus without harming intervening tissue. Its ability to focus the target of ablation at specific depths is an advantage over other energy modalities. Another advantage of HIFU technology is its mechanism of thermal ablation. Unlike all other energy sources that heat or cool tissue by thermal conduction, HIFU ablates tissue by directly heating the tissue in the acoustic focal volume, and is therefore much less affected by the "heat sink" of the circulating endocardial blood pool. The clinical studies utilizing HIFU have had mixed results.[23] There has been little independent experimental verification of the efficacy of HIFU devices to reliably create transmural lesions and long-term efficacy seems to be rather disappointing. The fixed depth of penetration of these devices may be a major problem in the wide range of thickness of pathologically altered atrial tissue.

In summary, each ablation technology has its own advantages and disadvantages. In the future, it will be imperative for surgeons to develop a more complete understanding of the effects of each surgical ablation technology and more carefully consider variations in atrial anatomy and electrophysiology. The effect of the applied technology on vital structures and on atrial function needs to be better delineated. This will allow for more appropriate use of devices in the operating room for each individual patient. While most of the devices have been shown to be efficacious in the arrested heart, few have shown the capability of creating reliable transmural lesions on the beating heart. This has to be considered in the era of the development of endoscopic and hybrid approaches attempting to evoke less invasive surgical ablation techniques.

## SURGICAL TECHNIQUES AND OUTCOMES

There are a variety of surgical procedures currently performed to ablate AF. They can be grouped into three broad categories: the biatrial CMP, left atrial lesion sets, and PVI.

Recently, new approaches have been developed for the treatment of lone AF. Epicardial lesions performed on the beating heart, including PVI and left atrial lesion sets, allow for an endoscopic approach without the need for cardiopulmonary bypass. Furthermore, a hybrid team approach with electrophysiologists applying endocardial catheter ablation techniques combines the promising success rates of epicardial surgical ablation with more sophisticated mapping to determine lesion integrity and evaluate results.

### The Cox-Maze IV Procedure

The CMP-IV can be performed through either a median sternotomy or a minimally invasive right minithoracotomy.[24] After initiating normothermic cardiopulmonary bypass, the right and left PVs are bluntly dissected. If the patient is in AF, amiodarone is administered and the patient is electrically cardioverted after a left atrial thrombus is ruled out by intraoperative transesophageal echocardiography. Pacing thresholds are obtained from each PV. Using a bipolar RF ablation device, the PVs are isolated by ablating a cuff of surrounding atrial tissue. Proof of electrical isolation is confirmed by demonstrating exit and/or entrance block from each PV.

The right atrial lesion set is performed on the beating heart (Fig. 43-3A). A single incision is usually made in the right atrial free wall, but recently a three-purse-string approach has been adopted to eliminate this incision in patients undergoing a minithoracotomy approach. All ablations are performed with the bipolar RF clamp except for two endocardial ablation lines to the tricuspid annulus. These are performed endocardially with a linear cryoprobe that is cooled to −60°C for 2 to 3 min.

The left-sided lesion set is performed via a standard left atriotomy under cardioplegic arrest (Fig. 43-3B). Our group has shown that isolating the entire posterior left atrium with connecting ablation lines between the upper and lower PVs, termed the box lesion set which resembles more closely the original CMP-III lesion set, resulted in a significantly higher drug-free freedom from AF at 6 and 12 months.[24] Cryoablation is used to connect the lesion to the mitral annulus and complete the left atrial isthmus line. It is important to remember that the coronary sinus needs to be ablated in line with the endocardial ablation in order to create the left atrial isthmus line. This is usually done with either the bipolar RF clamp or a linear cryoprobe placed epicardially over the coronary sinus. The left atrial appendage is amputated, and a final ablation is performed through the amputated left atria appendage into one of the left PVs. In patients undergoing a right minithoracotomy, cryoablation is more extensively applied to complete the posterior left atrial isolation and the left atrial appendage is oversewn from the inside.

#### OUTCOMES

A propensity analysis performed by our group has shown that there was no significant difference in the freedom from AF at 3, 6, or 12 months between the CMP III and IV groups.[25] However, the CMP IV has significantly shortened operative time and lowered complication rates while maintaining the high success rate of the original CMP III.[25,26] A Kaplan–Meier estimate of freedom from symptomatic AF for our entire CMP series was 85 percent at 10 years (Fig. 43-4). In 100 patients undergoing a stand-alone CMP-IV for lone AF (31 percent paroxysmal and 69 percent persistent or longstanding persistent AF), freedom from AF was 90 percent and freedom from AF off antiarrhythmic medication was 84 percent at 2 years with no intraoperative mortality and no postoperative strokes (Fig. 43-5).[27] Moreover, 84 percent of patients were free from anticoagulative therapy with warfarin. Failure was strictly defined in accordance with the recent consensus statement, whereby over two-thirds of

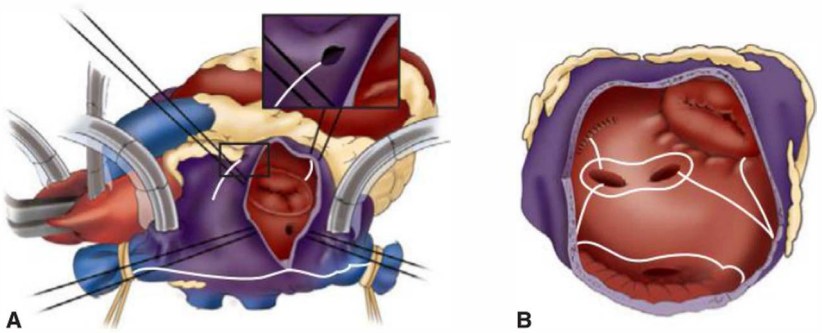



**FIGURE 43-3** **A.** Right atrial lesion set of the Cox-Maze procedure IV. **B.** Left atrial lesion set of the Cox-Maze procedure IV. (Reproduced with permission from Damiano RJ Jr, et al. The Cox maze IVprocedure: Predictors of late recurrence. *J Thorac Cardiovasc Surg* 2011;141:113–121. Copyright Elsevier.)

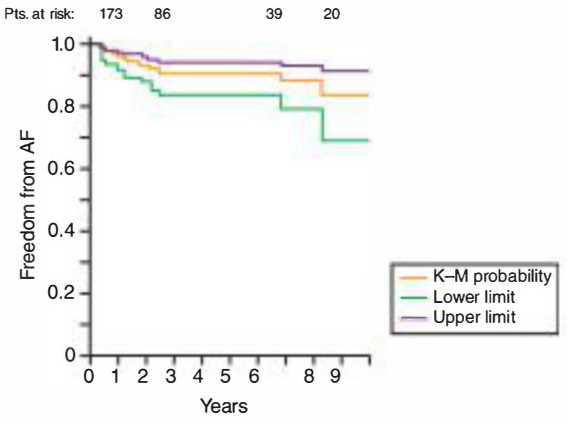



**FIGURE 43-4** Kaplan–Meier (K–M) analysis of freedom from atrial fibrillation (AF) for the Cox-Maze-Procedure (III + IV). Pts, patients. (Reproduced with permission from Weimar T, et al. The Cox-maze procedure for lone atrial fibrillation clinical perspective: A single center experience over 2 decades. *Circ Arrhythm Electrophysiol* 2012. Copyright Wolters Kluwer Health.)

patients had prolonged monitoring. In the entire CMP IV series, including concomitant cardiac procedures, the freedom from AF was 89 percent and the freedom from AF off antiarrhythmic drugs was 78 percent at 1 year.[12] There was also no difference in success rates for patients with paroxysmal compared with persistent or longstanding persistent AF.[12,27] An enlarged left atrial diameter, failure to isolate the entire posterior atrium with a complete box lesion set, and early atrial tachyarrhythmias were the predictors identified for late AF recurrence.

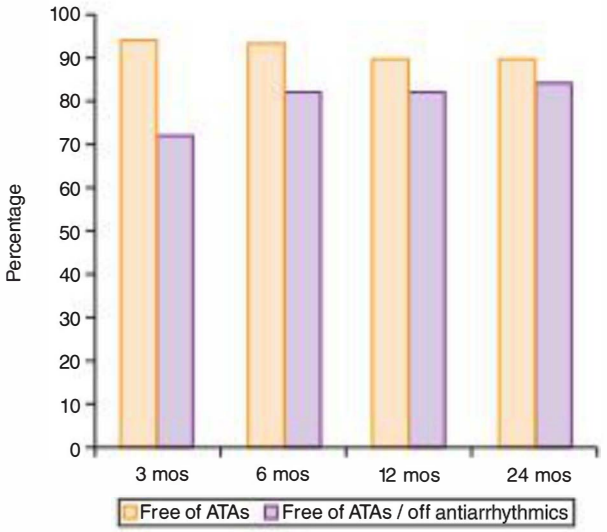



**FIGURE 43-5** Freedom from atrial tachyarrhythmias (ATAs) and freedom from ATAs off antiarrhythmic drugs following a stand-alone Cox-Maze IV procedure. (Reproduced with permission from Damiano RJ Jr, et al. The Cox Maze IV procedure: Predictors of late recurrence. *J Thorac Cardiovasc Surg* 2011;141:113–121. Copyright Elsevier.)

## Left Atrial Lesion Sets

Over the past decade, there have been a number of new surgical procedures introduced in an attempt to surgically treat AF. These procedures have generally involved some subset of the left atrial lesion set of the CMP. The results have been variable and have ranged from 20 to 90 percent rates of freedom from AF. They have been dependant on the technology used, the lesion set, and the patient population.

### OUTCOMES

A number of centers around the world have suggested performing ablation confined to the left atrium only to cure AF. This concept is supported by the fact that the majority of paroxysmal AF appears to originate around the PVs and the posterior left atrium. A left atrial lesion set typically involves PVI with an isthmus lesion to the mitral annulus as well as removal of the left atrial appendage. A myriad of ablation technologies has been used to create these lesion sets with a varied degree of success. There have been no randomized trials of biatrial versus left atrial ablation in the surgical population. Because of this, the importance of the right atrial lesions of the traditional CMP is difficult to determine. A meta-analysis of the published literature by Ad and colleagues revealed that a biatrial lesion set resulted in a significantly higher late freedom from AF when compared with a left atrial lesion set alone (87 vs 73 percent, $p = 0.05$).[28] This is not surprising considering the results of intraoperative mapping of patients with AF, showing that AF can originate from the right atrium in up to one-third of patients. In a rare randomized trail, Gaita and colleagues examined PVI alone versus two alternate left atrial lesion sets that both included an isthmus line. In this study, normal sinus rhythm at 2-year follow-up was only seen in 20 percent in the PVI group versus 57 percent in the other groups ($p < 0.006$).[29] Finally, our group has shown that isolating the entire posterior left atrium significantly improved drug-free freedom from AF at 6 months (54 vs 79 percent, $p = 0.011$) in a retrospective analysis.

## Pulmonary Vein Isolation—The Thoracoscopic Approach

PVI is an attractive therapeutic strategy because the procedure can be done without cardiopulmonary bypass and with minimally invasive techniques, utilizing either endoscopic approaches or small incisions. Based on the original report of Haïssaguerre, it has been documented that the triggers for paroxysmal AF originate from the PVs in many patients with lone AF. However, it important to remember that up to 30 percent of triggers may originate outside the PVs. This might be even more often the case in patients with structural heart disease. The PVs can be isolated separately or as a box. The most common technique described here utilizes an endoscopic, port-based approach to minimize incisional size and pain for the patient. At our institution, bipolar RF

clamps are favored to isolate the PVs, but unipolar RF and HIFU devices have been used as well.

Patients are intubated with a double-lumen endotracheal tube and external defibrillator pads are placed. A transesophageal echocardiogram is performed to confirm the absence of thrombus in the left atrial appendage. If a thrombus is found, the procedure is either aborted or converted to an open procedure, where the risk of systemic thromboembolism from left atrial clot can be minimized. An initial port for the thoracoscopic camera is usually placed at the fifth intercostal space. Under thoracoscopic vision, two small working ports can then be placed in the fourth and sixth intercostal spaces along the midaxillary line (Fig. 43-6). Under single-lung ventilation, the right phrenic nerve is identified and the pericardium is opened anterior and parallel to the phrenic nerve to expose the heart from the superior vena cava to the diaphragm. The space above and below the right PVs is dissected to allow enough room for insertion of an articulating dissector. The dissector and a guiding sheath are introduced and guided into the space between the PVs and the right pulmonary artery. After the dissector is removed, the sheath remains in place as a guide for the insertion of the bipolar RF clamp. At this point, the patient is cardioverted into sinus rhythm if needed so that pacing thresholds can be obtained. It is critically important to document entrance and/or exit block after ablation to confirm PVI. Some surgeons also use the opportunity provided by surgical exposure to detect and ablate ganglionic plexi (GP) at this time. High-frequency stimulation evokes a vagal response with bradycardia when applied to GP. The detected areas can be ablated until the vagal response diminishes. After pacing maneuvers are completed, the sheath is attached to the lower jaw of a bipolar RF clamp. The clamp is introduced into the chest, and the veins are clamped and ablated.

The approach to the left chest is similar to that to the right. The ports are positioned slightly more posterior than on the right side. The left phrenic nerve is identified, and the pericardium is opened posterior to the course of the nerve. The Ligament of Marshall is identified and divided. The dissector is then introduced and the guiding sheath is used to position the RF clamp around the left PVs as described above. After isolation, exit and/or entrance block is confirmed with pacing.

A major advantage of surgery is that the left atrial appendage can be addressed as well. This has been done by stapling across the base of the left atrial appendage with an endoscopic stapler or by placing an appendage-occluding device. After ablation of the left PVs and exclusion of the left atrial appendage, the left side of the pericardium must be closed to avoid herniation of the heart.



**FIGURE 43-6** Thoracoscopic port positioning for minimally-invasive pulmonary vein isolation.

### OUTCOMES

The results of PVI alone have been variable and dependent on patient selection. Different studies have shown encouraging results in patients with paroxysmal AF. Reports suggest a success rate between 80 and 89 percent in those patients after PVI. However, success rates decrease substantially in patients with persistent or longstanding persistent AF. Edgerton and colleagues reported only 56 percent of patients with persistent AF being free from AF at 6 months after PVI, with merely 35 percent being both free from AF and antiarrhythmics.[30] With concomitant procedures, the success rate of PVI is even worse. This is not surprising because those patients present with different underlying mechanisms for AF and a choice for PVI as a treatment option seems to be insufficient in most of those patients. There have been no randomized trials establishing the efficacy of GP ablation in increasing durable success rates. At our institution, we do not perform or recommend GP ablation. This is due to the lack of supporting data and the fact that our laboratory has shown reinnervation just 1 month following GP ablation in an experimental model.

## Thoracoscopic Left Atrial Lesion Set

There is wide consensus that the goal of developing less invasive procedures should not be at the cost of success rates. To address the shortcomings of PVI alone in many patients, new ablation devices have been developed allowing for an extension of the applied lesion set that can be performed thoracoscopically. Using a new generation of bipolar and unipolar RF devices, it is possible to perform a more extensive left atrial box lesion set epicardially through port access. In addition to the PVI technique described above, the transverse and oblique sinuses are dissected. This allows for a box lesion set to be performed isolating not just the PVs but the entire posterior left atrium. It is crucial that attention is paid to overlapping the lines of ablation from the right and the left side to avoid gaps and to complete a transmural roof lesion. An inferior line is created to connect the encircling ablation of the inferior right PV with that of the inferior left PV. Because it is impossible to perform a left atrial isthmus line epicardially, it is recommended to add a trigonal line of ablation from the

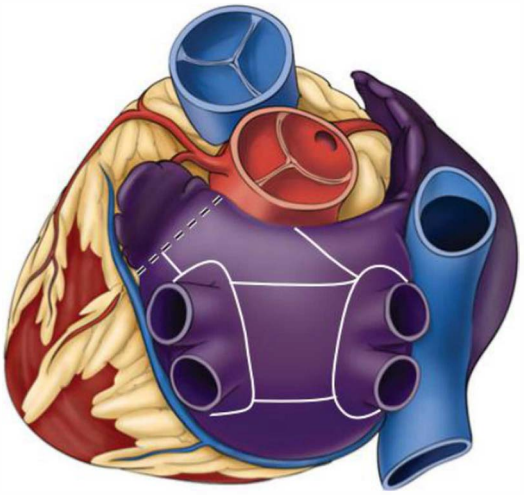


FIGURE 43-7 Endoscopic approach with extended left atrial lesion set.

isolated superior right PV to the aortic annulus (Fig. 43-7). To confirm conduction block of the ablation lines, pacing should be performed from within the box.

### OUTCOMES

Early results with an extended left atrial lesion set in addition to PVI have shown improved success, especially in patients with persistent AF compared with PVI alone. Sirak and colleagues reported a success rate of 87 percent off antiarrhythmic drugs after 6 months in 32 patients with persistent AF. In a larger series of almost 50 patients, Weimar and co-workers achieved success rates of about 90 percent freedom from AF and 85 percent freedom from AF off drugs at 12 month follow-up, independent of the type of AF, with no intraoperative complications or conversion to sternotomy. However, it is important to point out that it is technically challenging and more time-consuming to perform these extended lesions thoracoscopically and that proof of conductance block is mandatory for the box lesion set as well. This necessity to prove lesion integrity is due to the fact that there are still no devices on the market that reliably create linear transmural lesions on the beating heart except for the bipolar clamps. Also, it is important to note that acute demonstration of conduction delay or block does not guarantee a chronic block or transmural lesion. Demonstration of conduction delay can be difficult and may lead to misinterpretation even by experienced surgeons and electrophysiologists.

## The Hybrid Approach

The goal of the hybrid procedure is to combine the benefits of epicardially performed surgical ablation and endocardially performed catheter ablation in a dual approach. While thoracoscopic surgery is effective in isolating the PVs, addressing the Ligament of Marshall and managing the left atrial appendage, it has its limitations in effectively ablating atrial tissue, particularly the right and left atrial isthmus and the coronary sinus. Those areas can be addressed by catheter ablation if intraoperative mapping performed by the electrophysiologist shows gaps and conduction in one or more of these regions. Also, the success of creating transmural ablation lines can be confirmed by instantaneous mapping and by demonstrating conduction block using pacing. Possible gaps can then be closed by endocardial catheter ablation in the same setting (Fig. 43-8). Ideally, this procedure should be performed in a hybrid operating room. Because the underlying pathologic mechanisms are more complex in patients with persistent AF, this team approach may allow for a more patient-tailored

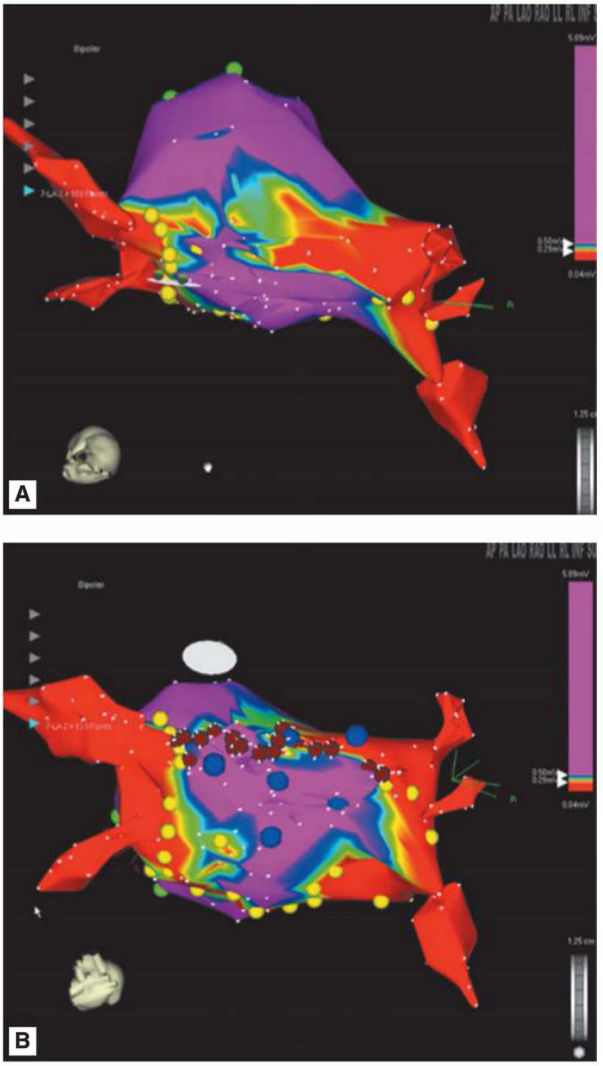



FIGURE 43-8 Intraoperative mapping during a hybrid procedure. **A.** Demonstration of gaps at the roof line after surgical ablation. **B.** Mapping after endocardial catheter ablation with closed gaps.

lesion set that more effectively prevents AF recurrence. A recent study from Allessie and colleagues has formed what they call the "Double Layer Hypothesis," where narrow wavelets in the endocardial and epicardial layers of the heart constantly feed each other in persistent AF. Although this has to be confirmed by further studies, it could add further support as to why hybrid ablation might be a promising approach for persistent AF.

### OUTCOMES

Only a few centers have reported on hybrid procedures. In many institutions it has been challenging to set up a team approach involving both electrophysiologists and surgeons. Edgerton and colleagues presented data on 12 patients with persistent AF who received hybrid ablation at the University of Virginia and University of Maastricht. At 12 month follow-up, 83 percent of patients were free from AF and off antiarrhythmic drugs. It is too early to comment on the efficacy or safety of the hybrid approach. Scientifically conducted trials are needed to evaluate any advantage over other ablation strategies.

## SUMMARY

In conclusion, the development of ablation technologies has dramatically changed the field of AF surgery. The replacement of the surgical incisions with linear lines of ablation has transformed a complex, technically demanding procedure into one accessible to the majority of surgeons. More importantly, these new ablation technologies have introduced the possibility of minimally invasive surgery for AF, prompting numerous efforts to develop simpler procedures that can be performed epicardially on the beating heart. There is already strong evidence that PVI may be effective in a subset of patients with paroxysmal AF. With extended lesions sets, it may be possible to extend the efficacy of minimally invasive procedures to patients with persistent and longstanding AF. However, surgeons must remember that the CMP has excellent efficacy in these patients and can be performed using a minithoracotomy with excellent success and low morbidity. It is imperative for surgeons who develop new procedures or lesion sets to carefully follow their results and to publish them in peer-reviewed journals. It also is mandatory to adhere to the recently published guidelines for follow-up of patients and for determining success or failure after these procedures. The biatrial CMP with 90 percent success rates in all types of AF still sets the benchmark for alternative lesion sets as well as for new and less invasive approaches currently under development.

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## SURGICAL THERAPIES FOR ATRIAL FIBRILLATION BOARD REVIEW QUESTIONS (CHAPTER 43)

1. Which is not a component of atrial fibrillation?
   A. A trigger
   B. Disordered AV nodal tissue
   C. Effective refractory period
   D. Conduction velocity
   E. Atrial anatomy

2. Which is correct regarding mechanisms of atrial fibrillation?
   A. Premature beats that trigger AF are only located in the pulmonary veins about 50 percent of the time.
   B. The conduction velocity within the pulmonary veins is faster than surrounding atrial tissue.
   C. The complex fiber orientation travels parallel within the pulmonary veins.
   D. Circus movement reentry is characterized by an activation that travels through the orifice of the pulmonary veins.
   E. Leading circle reentry requires an anatomic obstacle for the circuit.

3. Which is not associated with atrial fibrillation?
   A. Hypertension
   B. Aortic aneurysm
   C. Congestive heart failure
   D. Valvular heart disease
   E. Ischemic heart disease

4. Which of the following is not an indication for surgical ablation?
   A. A symptomatic patient with atrial fibrillation undergoing another cardiac surgical procedure
   B. An asymptomatic patient with atrial fibrillation undergoing another cardiac surgical procedure
   C. Stand-alone surgery after two failed catheter ablations
   D. A patient with atrial fibrillation and a left atrial appendage thrombus
   E. A patient with a contraindication to long-term anticoagulation and a CHADS score of 3

5. Which is true regarding outcomes after surgery for atrial fibrillation?
   A. Long-term freedom from AF after Cox-Maze IV for lone AF is 80 percent.
   B. One-year freedom from AF after Cox-Maze IV off antiarrhythmic medications is 80 percent.
   C. A biatrial lesion set does not improve late freedom from AF.
   D. Isolation of the entire posterior left atrium does not improve drug-free freedom from AF.
   E. Freedom from AF after PVI for paroxysmal AF ranges between 65 and 80 percent.

## ANSWERS

1. **Answer: B.** Atrial fibrillation requires both an initiating event (a trigger) and a permissive atrial substrate (altered refractory period, conduction velocity, or atrial anatomy). Disordered AV nodal tissue is not a component of atrial fibrillation.

2. **Answer: A.** Only 50 percent of triggers are found in the pulmonary veins. The conduction velocity within the pulmonary veins is slower than surrounding atrial tissue. The complex fiber orientation spirals perpendicularly around the veins. Circus movement reentry is characterized by an activation that travels around an anatomic structure. Leading circle reentry does not require an anatomic obstacle.

3. **Answer: B.** Hypertension, congestive heart failure, valvular heart disease, and ischemic heart disease are all associated with atrial fibrillation. Isolated aortic aneurysm is not associated with atrial fibrillation.

4. **Answer: D.** Presence of a left atrial appendage thrombus is not an indication for surgery. Any symptomatic or asymptomatic patient with atrial fibrillation undergoing another cardiac surgical procedure should be considered for concomitant surgical ablation. Stand-alone surgery should be considered in patients after one or more failed catheter ablations. A patient with a CHADS score of 2 or greater with a contraindication to anticoagulation should be considered for surgical ablation.

5. **Answer: B.** One-year freedom from AF after Cox-Maze IV off antiarrhythmic medications is 80 percent. Long-term freedom from AF after Cox-Maze IV for lone AF is 90 percent. A biatrial lesion set and isolation of the entire posterior left atrium both significantly improve late freedom from AF. Freedom from AF after PVI for paroxysmal AF ranges between 80 and 90 percent.

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44

# Pacemaker and Defibrillator Therapy in Cardiac Surgery Patients

*Brad S. Sutton*
*Kenneth C. Bilchick*
*Ronald D. Berger*

**KEY CONCEPTS**

- Pacemaker therapy effectively treats bradycardia-related symptoms for patients with sinus node dysfunction, advanced atrioventricular (AV) block, and in some instances carotid sinus hypersensitivity.
- Conduction disturbance after cardiac surgery is relatively common after coronary artery bypass grafting and valve surgery. Although the natural history of postoperative AV block is variable, the need for a permanent pacemaker (PPM) system is higher in those with preexisting electrocardiogram abnormalities, prolonged bypass time, and repeat procedures.
- Bradycardia after cardiac transplantation is usually temporary and far less common with bicaval anastomoses.
- In carefully selected heart failure patients, cardiac resynchronization therapy (CRT) has been shown to improve heart failure symptoms, quality of life, and reduce mortality.
- Several randomized clinical trials have demonstrated reduced infectious complications following permanent device implantation with empiric periprocedural antibiotic administration.
- When coronary sinus anatomy or pacing parameters prohibit transvenous lead placement for CRT, a number of techniques can be used to place epicardial leads. Robotic arm placement may reduce the amount of postoperative pain that patients experience.
- Optimal PPM therapy requires selection of appropriate pacemaker type and pacing mode for each patient.
- Pacemaker complications can be divided into those associated with the implantation procedure, subsequent infections, loss of lead integrity, and programming-related problems.
- Indications for device extraction include systemic infection, arrhythmia or other complications related to retained fragments or leads, and the need for additional vascular access.
- Implantable cardioverter-defibrillator therapy is indicated for patients with structural heart disease and life-threatening ventricular arrhythmias or risk factors for sudden death.

## INTRODUCTION

Permanent pacemakers (PPMs) were introduced in the 1950s for use in patients with pathologic conditions of the sinus node, atrioventricular (AV) node, or His–Purkinje system. Since that time they have been refined to allow more complex programming. In addition, periprocedural morbidity has been reduced significantly. As a result, the number of devices implanted has increased steadily, with over 150,000 new pacemakers implanted in the United States each year.[1]

## ANATOMY OF THE CONDUCTION SYSTEM

The sinus node is an oval piece of tissue in the roof of the right atrium that is 10 to 20 mm long and 2 to 3 mm wide. It is less than 1 mm from the epicardial surface between the superior and inferior venae cavae.[2,3] Its blood supply is derived from the right coronary artery (RCA) 55 to 60 percent of the time and from the circumflex coronary artery 40 to 45 percent of the time.[2]

The atria are anatomically complex structures and differ significantly from each other. The right atrium is heavily trabeculated over the lateral wall and appendage and is characterized by significant heterogeneity, with abrupt changes in muscle fiber orientation over short distances. In contrast, the left atrium is a more uniform structure. Unlike ventricular myocardium, which contains Purkinje fibers, it now is generally accepted that the atria do not contain specialized conduction tissue. Instead, the spread of the impulse depends on the properties of the atrial muscle bundles. Simultaneous electrical mapping of canine left and right atria demonstrate that the left atrium consistently activates approximately 10 ms later than does the right atrium. Rapid activation of the anterior surface of the left atrium is facilitated by a muscle bundle known as Bachmann bundle. The wave fronts then converge in the posterior left atrium inferior to the pulmonary veins. Human atria demonstrate similar activation patterns, although the activation times are twice as long because of the larger atrial surface area.[3]

The compact portion of the AV node (AVN) is just beneath the right atrial endocardium anterior to the coronary sinus ostium and directly above the insertion of the septal leaflet of the tricuspid valve (TV). The AVN is located at the apex of the triangle of Koch, which is defined by the TV inferiorly, the tendon of Todaro superiorly, and a line drawn between the coronary sinus and the tricuspid annulus posteriorly. Of note, the node is well removed anteriorly from the coronary sinus. The AVN becomes the penetrating bundle of His at the central fibrous body. In 85 to 90 percent of people, the blood supply to the AVN is via the RCA; in the remainder, blood is supplied via the circumflex coronary artery.[2]

The branching portion of the His bundle begins at the muscular intraventricular septum and becomes the left

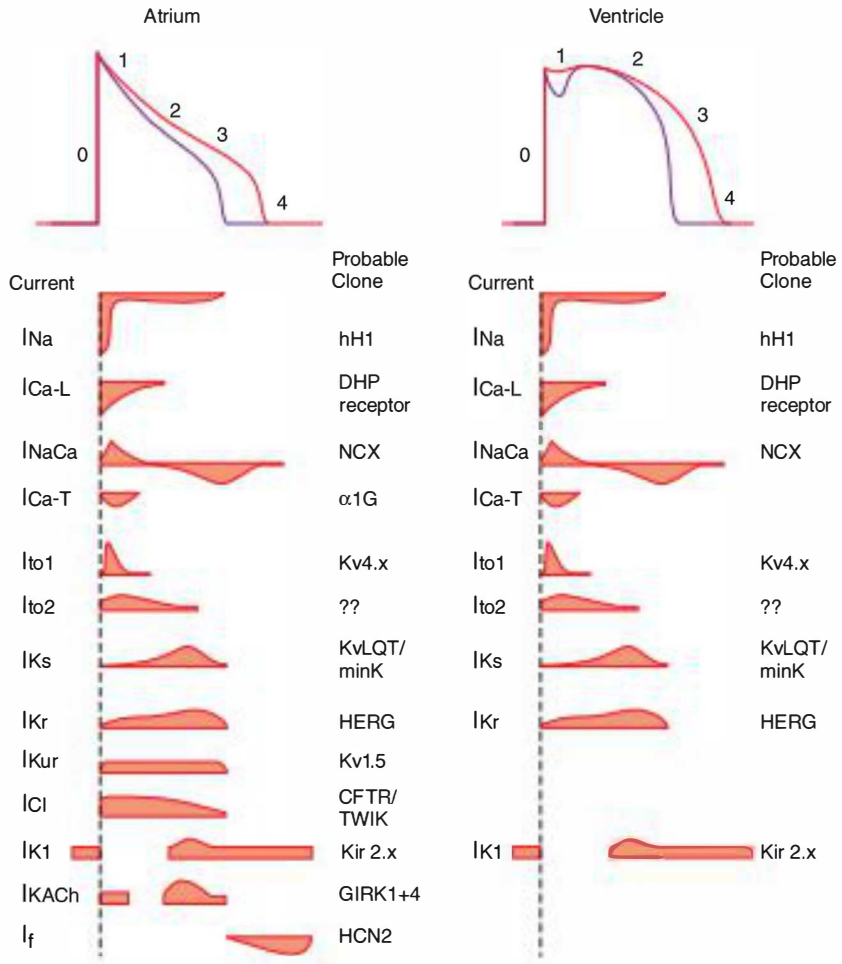



**FIGURE 44-1** Atrial and ventricular action potentials. Schematic of inward and outward ionic currents, pumps, and exchangers that underlie atrial and ventricular action potentials in the mammalian heart. Control and failing (*red line*) action potential profiles are shown on top. Each phase of the action potential is labeled. Under the action potentials, a schematic of the time course of each current is shown, and the gene product (probable clone) that underlies the current is indicated. (Reproduced with permission from Akar FG, Tomaselli GF. Genetic basis of cardiac arrhythmias. In: Fuster V, Alexander A, O'Rourke RA (eds). *Hurst's the Heart*, 11th ed. New York: McGraw-Hill, 2004.)

bundle branch (LBB) and the right bundle branch (RBB). The LBB arises and continues onto the septum beneath the noncoronary cusp of the aortic valve. The LBB may divide into anterior and posterior branches or may have a different branching pattern. The RBB continues as an unbranched extension of the AVN and continues along the right side of interventricular septum to the apex of the right ventricle (RV) and the base of the anterior papillary muscle. Purkinje fibers continue from the bundle branches as networks of conduction fibers on the endocardial surface of both ventricles.[2]

## ELECTRICAL PRINCIPLES OF CARDIAC PACING

The conducting tissues of the heart may be divided into fast-response and slow-response tissues. The distribution of ions and their associated electrical voltage gradients are responsible for the cardiac action potential. The baseline of this potential is −90 mV, and the peak is +20 mV for fast-response tissues (Fig. 44-1). The depolarization of fast-response tissues such as the atria, the bundle of His, bundle branches, and Purkinje fibers is due to an inward sodium current, whereas repolarization of those tissues is due primarily to outward potassium currents. In slow-response tissues such as the sinus node and the AVN, the baseline is about −70 mV and depolarization depends primarily on the L-type calcium current.

Cardiac pacing is based on the principle that myocardial cells can be depolarized repeatedly by electrical stimulation. In cardiac pacing, voltage is applied across two electrodes, at least one of which is in contact with myocardium. In bipolar leads, the two electrodes usually are separated from each other on the lead by about 1 cm. In unipolar leads, only one electrode is in contact with the myocardium, and the other electrode is typically the outer can of the pacemaker generator.

The voltage, current, resistance, and energy of a pacing system are related to one another according to the following equations:

$$V = I \times R$$

where $V$ = voltage (volts), $I$ = current (milliamperes), and $R$ = resistance (kilohms).

$$E = V \times I \times t \text{ (time the current is applied) or}$$
$$E = (V^2/R) \times t$$

Electrical sensing is based on the detection of the intrinsic current between the two electrodes on bipolar leads or between the lead tip and the pacemaker generator in a unipolar system, with a filter system in place. Unipolar systems are subject to much more noise and/or cross talk than are bipolar leads because the distance between the two electrodes is greater.

## CLINICAL INDICATIONS FOR PACING

### Indications for Permanent Pacing

Current indications for permanent pacing are based on the 2008 consensus guidelines published by the ACC/AHA/HRS.[4] The indications follow the standard evidence-based tiered system. A class I indication means that a procedure generally is agreed to be beneficial; class IIa indications are those for which there is conflicting evidence or a divergence of opinion but the weight of evidence is in favor of a procedure. Class IIb is similar to class IIa except that the efficacy of a procedure is less well established.

Permanent pacing should be considered for all patients with irreversible symptomatic bradycardia and selected patients with asymptomatic bradycardia. In addition, indications for cardiac resynchronization therapy (CRT) via biventricular pacing in patients with dilated cardiomyopathies have increased significantly in recent years. Pacing needs in specific cardiac operations are considered individually later in this section but are based on the general indications given below.

Common causes of symptomatic bradycardia include sinus node dysfunction (SND), third degree or advanced second degree AV block (AVB), and carotid sinus hypersensitivity (CSH). The following is a summary of the recommendations for PPM implantation in each of these conditions[4]:

- Class I recommendations for pacing in SND:
  - SND with documented symptomatic bradycardia
  - Symptomatic chronotropic incompetence
  - Symptomatic bradycardia that results from required drug therapy for medical conditions
- Class I recommendations for pacing in acquired AVB:
  - Third degree or advanced second degree AVB with symptomatic bradycardia
  - Third degree AVB that results from required drug therapy for medical conditions
  - AVB in symptom-free patients in sinus rhythm with asystole >3 s, escape rhythm <40 bpm, or infranodal escape
  - AVB in symptom-free patients in AF with pauses >5 s
  - Postoperative AVB that is not expected to resolve after surgery
  - Mobitz II second degree AVB
  - Alternating bundle branch block
- Class I recommendations for pacing for CSH:
  - Syncope occurring due to spontaneous CSH and carotid sinus pressure that induces ventricular asystole >3 s

### Permanent Pacing After Coronary Artery Bypass Grafting

After coronary artery bypass grafting (CABG) or valve surgery, patients may develop a number of conduction

disturbances, including a left hemiblock, right bundle branch block (RBBB), left bundle branch block (LBBB), bifascicular block, and AVB. The overall incidence of conduction disturbances after CABG is reported to be 10 to 15 percent.[5,6]. The significance of the various fascicular blocks after CABG has been controversial. In contrast to some early studies from the 1970s and 1980s, more recent studies of patients after CABG have not demonstrated any association between bundle branch block or intraventricular conduction defects and cardiac mortality over 3 to 5 years[7–9] even though these conduction disturbances probably indicate some degree of intraoperative myocardial damage.

It has been estimated that overall, 0.4 to 1.1 percent of patients who undergo CABG will require permanent pacing.[6] This risk is roughly doubled for patients undergoing repeat operations.[10] Risk factors for AVB and other conduction disturbances include advanced age, the number of vessels bypassed, left main coronary artery stenosis accompanied by total occlusion of a dominant RCA, the presence of an ungraftable RCA, proximal left anterior descending artery (LAD) stenosis involving the first septal perforator, aortic cross-clamp time, and prolonged hypothermic cardioplegia.[11–15] In one series of 120 consecutive cardiac surgery patients, the risk of postoperative pacemaker implantation was higher for patients with preexisting clinical or electrocardiogram (ECG) evidence of a conduction disturbance. In this study, predictors of long-term pacemaker dependency were postoperative complete AVB and bypass time >120 min.[16] Of note, the use of normothermic cardioplegia for shorter periods may be responsible for the decreased incidence of AVB after CABG in some series.[17]

The natural history of AVB in patients after CABG is that it may resolve within hours after the surgery; last for days, weeks, or months and then resolve; or persist.[11,12] In a series of 348 consecutive patients undergoing CABG, 56 of whom developed AVB postoperatively, the AVB lasted for less than 6 h in 32 (57 percent) and for more than 6 h in 24 (43 percent).[13] In another series of 93 consecutive patients undergoing CABG, all four patients who developed third-degree AVB after the operation were no longer in AVB after 2 months (AVB resolved in one patient on the second postoperative day; the other three patients had PPMs implanted before discharge).[11] Another study evaluated 26 patients who had a PPM implanted for AVB and 10 patients with a PPM implanted for SND after CABG. The pacemaker dependency rate (defined as the need for pacing with mode set to VVI 50) after 3 years was 65 percent for the AVB group and 30 percent for the SND group.[12] If the AVB resolves, permanent pacing is unnecessary. Although it may be reasoned that selected patients may not need a generator change at the time of battery end of life because of potential recovery of the conduction system, the authors generally maintain the PPM in most patients because it is difficult to establish with certainty that these patients will not require pacing at some point in the future. Furthermore, it should be noted that a generator change is a very low-risk procedure.

## Permanent Pacing After Valvular Surgery

Compared with the approximately 1 percent of patients undergoing CABG who have a need for permanent pacing, 3 to 6 percent of patients undergoing valve surgery require permanent pacing.[6,18] The most likely reason for the increased need for permanent pacing after valve surgery is the risk of trauma to the conduction system with this procedure. An estimation of the likelihood of the need for permanent pacing at the time of surgery informs the choice of the temporary epicardial pacing configuration. Since temporary leads may be associated with bleeding, tamponade, bypass graft injury, and infection, only the necessary number of leads should be implanted. For example, whereas a single ventricular epicardial lead may be appropriate for a low-risk patient, a dual-lead configuration with an additional ventricular lead (in case one lead fails) may be appropriate for higher risk patients.

In a series of 4694 patients undergoing valve surgery between 1992 and 2002 at the Brigham and Women's Hospital, a multivariate analysis established the following as risk factors for conduction disturbances requiring PPM implantation: RBBB [odds ratio (OR) 3.6], LBBB (OR 2.0) and PR interval more than 200 ms (OR 1.9) on the preoperative ECG, multivalve surgery involving the TV (OR 3.7) or not involving it (OR 2.1), advanced age (OR 1.4), and a history of prior valve surgery (OR 1.8).[18] For surgery involving only one valve, the risk was lowest for mitral valve surgery (3.5 percent), somewhat higher for aortic valve surgery (5.1 percent), and highest for TV surgery (12 percent). On the basis of the preoperative ECG, the need for permanent pacing was greatest in those with a preexisting isolated RBBB (18 percent) or an RBBB accompanied by a left hemiblock (bifascicular block; 16 percent) and somewhat lower in those with a preexisting LBBB (10 percent). A prediction rule for the need for permanent pacing was developed according to the point system shown in Table 44-1. The need for permanent pacing for total point scores of 0, 1, 2, 3, 4, 5, and 6 was 1.9, 5.2, 8.7, 12, 21, 36, and 50 percent, respectively.[18] In a recent retrospective review of 4999 patients undergoing cardiac surgery between 1993 and 2005, the strongest predictors of pacemaker implantation were LBBB and aortic valve surgery. TV repair was not associated with an increased rate of pacemaker implantation, though these patients made up a minority of the cases (7 percent).[19] Similar to coronary bypass surgery, repeat valve replacement operations are associated with increased risk of long-term conduction disturbance, requiring a PPM in as many as 16 percent of patients.[10] A better understanding of what constitutes a high-risk patient will help providers avoid delays in PPM implantation and facilitate patient mobilization and discharge.

## Prophylaxis for Postoperative Atrial Fibrillation

Postoperative atrial fibrillation occurs in 10 to 40 percent of all patients undergoing open heart surgery.[20–23] The issue of

**TABLE 44-1: Risk Score to Predict Permanent Pacing After Valve Surgery**

| Variable | Points |
|---|---|
| Preoperative electrocardiogram | 2 |
| Right bundle branch block | 1 |
| Left bundle branch block | 1 |
| PR interval >200 ms | |
| Multivalve surgery | 2 |
| Tricuspid valve included | 1 |
| Tricuspid valve not included | |
| Other | 1 |
| Age 70 years or above | 1 |
| Prior valve surgery | |

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prophylactic pacing after cardiac surgery as prophylaxis for atrial fibrillation was addressed in a meta-analysis of eight trials that enrolled a total of 776 patients and compared control patients with patients randomized to right atrial, left atrial, or biatrial pacing.[24] The patients could be paced at a fixed high rate (fixed high-rate pacing) or at a rate just fast enough to overcome the intrinsic rate (overdrive pacing). Risk reductions for postoperative atrial fibrillation of 2.6-fold and 1.8-fold were found for overdrive biatrial and right atrial pacing, respectively, and there was a 2.5-fold reduction for fixed high-rate biatrial pacing. Whether biatrial pacing confers an advantage over right atrial pacing is controversial.[25,26] Ongoing studies should help clarify these issues. Although temporary atrial pacing to decrease atrial fibrillation after cardiac surgery has gained general acceptance, the data supporting permanent pacing are not well established.

Although medical therapy with prophylactic β-blockers, amiodarone, and sotalol has been shown to reduce postoperative atrial fibrillation, pacing therapy offers several advantages, including minimal expense; no association with ventricular proarrhythmia, bradycardia, or hypotension; and no need for the initiation of therapy before surgery. In summary, the approximately 2.5-fold risk reduction associated with biatrial pacing (either overdrive or fixed high rate) and overdrive right atrial pacing makes pacing an attractive nonpharmacologic method for preventing atrial fibrillation after cardiac surgery, particularly since atrial epicardial wires are in place.

## Pacing in Cardiac Transplantation

Bradycardia after cardiac transplantation is common, usually temporary, and often due to SND. Although the most common cause for this SND is probably surgical trauma at the time of transplantation,[27] several other causes have been implicated, including disruption of the blood supply to the sinus node,[28] ischemic time,[29] rejection,[30] donor age,[31] and pretransplant amiodarone use.[32]

Until the early 1990s, the standard anastomosis between the recipient and donor hearts was a biatrial anastomosis, as originally described by Lower and Shumway in the canine heart in 1960.[33] As the biatrial anastomosis requires opening the recipient right atrium from the inferior vena caval (IVC) orifice with transection and oversewing of the recipient superior vena cava (SVC), the suture line may result in direct damage to the donor sinus node as well as the blood supply to the sinus node.[34] In the bicaval anastomosis, which came into widespread use in the 1990s, there are direct donor–recipient anastomoses of the IVC and SVC, although the left-sided anastomosis may occur at the level of the pulmonary vein or left atrium, depending on the technique used.[35,36] As might be expected, several studies have documented a decreased need for pacing with the use of the bicaval anastomosis compared with the standard biatrial anastomosis.[34,37–39] In the two randomized studies that compared the need for permanent pacing on the basis of the type of anastomosis used, permanent pacing was required in 5 (6.5 percent) of 75 patients with the biatrial anastomosis but was not required in any of the 81 patients with the bicaval anastomosis. According to a compilation of six studies, permanent pacing was required in 60 (9.2 percent) of 651 patients with biatrial anastomoses compared with only 1 (0.3 percent) of 340 patients with bicaval anastomoses. Although the incidence of prolonged SND has been reduced with bicaval anastamoses, this benefit may be attenuated in the era of extended donor criteria. Posttransplant PPM requirements were examined in 88 patients who underwent a bicaval anastamotic approach between 2000 and 2004. Ultimately, 18 of the 88 (20.5 percent) required PPM implantation. Mean donor age was the major risk factor for postoperative pacemaker requirement (44.7 years vs 35.7, $p = 0.0289$) and may suggest a predilection for increased susceptibility to perioperative ischemia and a higher incidence of underlying conduction and coronary disease in older hearts.[40]

The initial approach to a cardiac transplant patient with postoperative bradycardia resulting from SND is medical therapy with chronotropic agents and the use of operatively placed temporary epicardial leads if necessary. Theophylline has been shown to improve prolonged chronotropic dysfunction in transplant recipients and is the drug of choice.[41] Isoproterenol and terbutaline also may be used. Published commentaries generally have recommended permanent pacing if bradycardia caused by SND persists for 2 to 3 weeks.[34,42] Ambulatory Holter monitoring may aid in the decision whether to implant a PPM. The reason to wait as long as possible to implant a permanent system is that SND after transplantation is usually manifest by the first week and resolves over 1 to 3 months. Serial electrophysiologic studies in 40 posttransplant patients demonstrated that the sinus node recovery time (SNRT) became abnormal by the first week in 6 (15 percent) patients and by 3 months in 1 other patient. In all six patients with early SND, the SNRT returned to normal

by 6 weeks, although sinoatrial conduction abnormalities persisted in two patients.[43] Because maintaining AV synchrony will maximize cardiac output, a dual-chamber pacemaker system usually is used and programmed to DDDR, although permanent atrial pacing without a ventricular lead is an option (albeit one rarely used in the United States) if AV conduction is intact. One advantage of using an atrial lead only is the decreased likelihood of dislodgment with biopsy, although this is uncommon with experienced operators. If a biatrial anastomosis is present, the pacemaker lead should be implanted in the anteroseptal right atrium rather than the lateral right atrium near the anastomosis.

## Cardiac Resynchronization Therapy (Biventricular Pacing)

Heart failure is the fastest growing cardiovascular diagnosis in the United States with an estimated prevalence of 2.5 percent in adults and an estimated cost of over $39.2 billion in 2010.[44] Heart failure syndromes represent a constellation of molecular, anatomic, and neurohormonal perturbations. One downstream effect of neurohormonal regulation includes the alteration of myocardial membrane properties leading to action potential prolongation, an imbalance of calcium homeostasis, and cell–cell coupling. These changes ultimately lead to interventricular dyssynchrony (often LBBB) and greater arrhythmogenicity. Although great strides have been made using medications to target and attenuate the negative remodeling process that ensues with heart failure, biventricular pacing to restore cardiac synchrony provides another arrow in the quiver to combat heart failure morbidity and mortality.

CRT has proven beneficial for patients with dilated cardiomyopathy, intraventricular conduction delay, and heart failure. The objective is to correct dyssynchrony by pacing the left ventricle alone or both ventricles (biventricular).

The Multisite Stimulation in Cardiomyopathy (MUSTIC) study showed statistically significant improvements in the 6-min walk and quality of life (but not mortality) with biventricular pacing,[45] and the Multisite InSync Randomized Clinical Evaluation (MIRACLE) study has shown improvements in functional class, quality of life, and left ventricular (LV) dimensions.[46] Resynchronization therapy in the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial directly compared pacing with (CRT-D) and without (CRT-P) defibrillation capability with optimal medical therapy.[47] CRT-D reduced mortality by 36 percent compared with medical therapy, but there was insufficient evidence to conclude that CRT-P was inferior to CRT-D. The effects of CRT on mortality were further evaluated in the CARE-HF trial. Enrollment criteria included New York Heart Association (NYHA) class III/IV heart failure, LVEF <35 percent, QRS ≥120 ms. In both trials the risk of death was reduced with CRT versus no pacing; however, only CARE-HF demonstrated statistical significance (HR 0.64, $p$ <0.002).[47,48] No large trial has yet demonstrated clinical benefit among patients without QRS prolongation, even when they have been selected for echocardiographic measures of dyssynchrony.[49]

The benefit for implantable cardioverter-defibrillator (ICD) implantation in heart-failure patients has been well established based on SCDHeFT and MADIT-II data showing a survival benefit with defibrillators in patients with class II or III heart failure and a severely depressed ejection fraction.[50–52] More recently, the MADIT-CRT trial compared the use of a CRT plus an ICD device versus an ICD alone in 1820 patients with NYHA class I or II heart failure, LVEF ≤30 percent, and QRS ≥130 ms. This study included both ischemic and nonischemic cardiomyopathy patients and demonstrated a reduction in the primary combined endpoint of death or heart failure events in the CRT-D group (17.2 vs 25.3 percent, $p$ = 0.001). This was driven primarily by a 41 percent reduction in heart failure events.[53]

Based on these data, current guidelines recommend CRT with biventricular pacing in patients with NYHA class III or ambulatory class IV heart failure, LVEF of 35 percent or less, and a QRS duration greater than 120 ms,[4] or NYHA class I or II with LVEF ≤30 percent and QRS ≥130 ms.

Since the left ventricle is usually paced via the coronary sinus, transvenous LV pacing is more technically difficult than is endocardial right ventricular pacing. A number of challenges exist with coronary sinus lead placement including difficulty accessing the coronary sinus ostium, unfavorable venous anatomy, and poor pacing parameters owing to myocardial fibrosis, or extracardiac stimulation. Transvenous coronary sinus leads can ultimately be placed successfully about 90 percent of the time. For the remaining cases, an alternative approach may be used such as surgical epicardial placement or transseptal or transapical LV endocardial placement, as discussed below.

## Hypertrophic Obstructive Cardiomyopathy

The objective of permanent pacing in patients with hypertrophic obstructive cardiomyopathy is to improve outflow obstruction with early stimulation of the right ventricular apex. The pacemaker is generally programmed to DDD mode with leads in the right atrium and RV. Randomized clinical studies[54–56] have shown statistically significant reductions in the LV outflow tract pressure gradient but only mild improvement in functional status and generally no improvement in quality of life. There are currently no data available to suggest that pacing changes the natural history of hypertrophic cardiomyopathy (HCM). Therefore, routine implantation of dual-chamber pacemakers should not be advocated in all patients with symptomatic obstructive HCM. Patients who may benefit the most are those with significant gradients (more than 30 mm Hg at rest or more than 50 mm Hg provoked). Myomectomy and ethanol septal ablation are probably more effective treatment options for patients with hypertrophic obstructive cardiomyopathy. Complete heart block can develop after transcoronary alcohol ablation

of septal hypertrophy in patients with HCM and should be treated with permanent pacing. The decision whether to implant a pacemaker alone or a pacemaker–defibrillator is based on clinical judgment but may be guided by several factors that, if present, favor a pacemaker–defibrillator. These factors are a personal history of syncope or sudden cardiac death, a family history of sudden cardiac death, nonsustained ventricular tachycardia (VT), massive hypertrophy (wall thickness of 30 mm or more), a pathologic drop in blood pressure with exercise, and HCM mutations associated with an increased risk for sudden cardiac death.

### Pacing After a Myocardial Infarction

In patients who have had a myocardial infarction, temporary pacing is a class I indication for the following conditions[4]:

1. Asystole
2. Symptomatic bradycardia
3. Bilateral BBB [alternating BBB or RBBB with alternating left anterior/posterior fascicular block (LAFB/LPFB)]
4. Asymptomatic Mobitz 2 AVB
5. New bifascicular block (LBBB or RBBB with left hemiblock)

Permanent pacing is a class I indication for the following conditions[4]:

1. Persistent second-degree AVB in the His–Purkinje system with alternating bundle branch block or third-degree AVB within or below the His–Purkinje system after ST-segment elevation MI. (Level of Evidence: B)
2. Transient advanced second- or third-degree infranodal AVB and associated bundle branch block. If the site of block is uncertain, an electrophysiological study may be necessary. (Level of Evidence: B)
3. Persistent and symptomatic second- or third-degree AVB. (Level of Evidence: C)

Permanent pacing usually is not indicated after a myocardial infarction for transient second- or third-degree AVB in the absence of a wide QRS (e.g., with an isolated LAFB). The long-term prognosis for survivors of myocardial infarction who have had AVB is related primarily to the extent of myocardial injury and the character of intraventricular conduction disturbances rather than the AVB itself.

## PACEMAKER LEADS AND TECHNIQUES FOR IMPLANTATION

### Temporary Endocardial Leads

Temporary endocardial leads usually are introduced via a sheath system in a jugular or subclavian vein. The right internal jugular vein is generally the vein of choice, as it allows for easy passage of the pacing lead through the right atrium and into the RV. As these leads usually are placed in the intensive care unit, often without the aid of fluoroscopy, the position of the lead initially is gaged by viewing the intracardiac electrogram (the distal end of the pacing lead is attached to a cardiac monitoring system). As the lead traverses the right atrium and tricuspid annulus, a large amplitude P wave will transition to a large R wave. Premature ventricular beats and injury current indicate that the lead is in contact with the right ventricular myocardium. A common pitfall is pacing the tricuspid annulus. Because this is an unstable position, the lead should be advanced amply into the RV. After the introduction of the lead and verification of appropriate pacing thresholds, the lead should be locked into place in the sheath and its position should be verified with chest radiography.

### Permanent Endocardial Leads

Endocardial leads may be fixated actively or passively. The technique for the introduction of permanent endocardial leads is discussed in detail below. In active fixation, a screw mechanism attaches the lead to the endocardium. Passive fixation leads have polyurethane or silicon tines that facilitate attachment to trabeculae. Passive atrial pacemaker leads are designed for placement in the trabeculations of the right atrial appendage. Passive ventricular leads are designed for placement in the apex of the RV with its trabeculations. Placement of leads in other areas of the atrium and ventricle generally requires active fixation for stabilization. Pacing thresholds may be slightly higher with active fixation, although this is rarely of any consequence. Pacing thresholds may increase after active fixation as a result of inflammation and fibrosis at the site of injury. Most leads are now laden with steroids to minimize the inflammatory response. Active fixation leads are more likely to perforate, particularly at the RV apex, but passive leads may have higher rates of acute dislodgement, particularly in the atrium. Active fixation leads are thought to be easier to extract, though little data exists to support this. In general, the two leads have similar sensing characteristics.

### Technique for Implantation of Permanent Endocardial Leads

The subclavian approach is currently the standard approach for the placement of endocardial leads and is used for the placement of over 75 percent of those leads.[1] This approach has evolved since Furman and Schwedel[57] reported successful transvenous endocardial pacing via the brachial vein in 1959. Because of a high rate of lead dislodgement, this approach was replaced briefly by the external jugular vein approach.[58] The cephalic cut-down approach became the standard in the late 1960s[59] and remained the standard for over a decade. As a result of the introduction of the peel-away sheath for the percutaneous introduction of leads, the subclavian approach emerged and remains the standard.[60] In a series of 200 consecutive patients randomized to endocardial lead insertion via a subclavian approach or a cephalic approach, successful lead placement was achieved in 99 percent randomized

to the subclavian approach and 64 percent of cases with the cephalic approach.[61] The total procedure time was 86 ± 22 min with the subclavian approach and 98 ± 35 min with the cephalic approach ($p$ <0.01). Blood loss was also less with the subclavian approach (55 ± 13 mL vs 115 ± 107 mL; $p$ <0.01).

The following approach is adapted from Calkins and coworkers and is used at the authors' institution[61]:

1. The patient is positioned supine on the fluoroscopy table and a venogram is performed to guide vascular access. Approximately 10 mL of 1:1 contrast dye and normal saline solution is injected via an intravenous (IV) line placed distally in an ipsilateral vein and then flushed with 25 to 50 mL of saline.
2. A sterile field is created.
3. Generous local anesthesia is given (this may be sufficient, but light sedation often is needed).
4. A subcutaneous generator pocket is created by an incision 2 cm below and parallel to the clavicle. The pocket is created along the pectoralis fascia (Fig. 44-2).
5. Once the axillary and subclavian veins have been opacified, a 5F-micropuncture needle attached to extension tubing and a 10-mL syringe is positioned at a 60° angle to the plane of the skin and parallel to the axillary vein (Figs. 44-3 and 44-4). Adjustment of the site of needle entry may be necessary to ensure that the needle enters the vein as it crosses over the first rib.
6. A micropuncture guidewire is advanced through the needle to the SVC and is replaced by a 5F-micropuncture sheath that allows the introduction of a 50-cm, 0.035-in J-tipped guidewire.
7. A peel-away sheath (generally 7–9F) is advanced over the 0.035-in guidewire.
8. The ventricular lead is advanced through this sheath, and the sheath then is peeled and removed. The ventricular lead is advanced into the right ventricular apex under fluoroscopy.

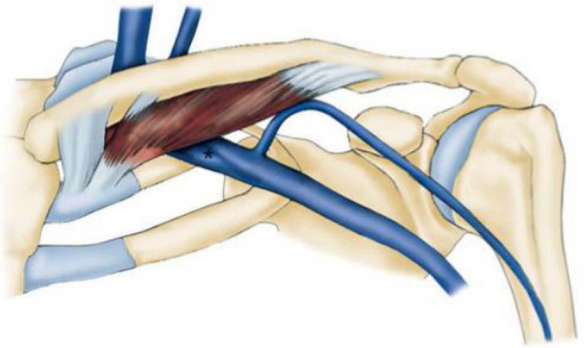


**FIGURE 44-3** Left subclavian vein and associated anatomic structures. (Reproduced with permission from Calkins H, Ramza BM, Brinker J, et al. Prospective randomized comparison of the safety and effectiveness of placement of endocardial pacemaker and defibrillator leads using the extrathoracic subclavian vein guided by contrast venography versus the cephalic approach. *Pacing Clin Electrophysiol* 2001;24:456–464. Copyright © John Wiley & Sons.)

9. If an atrial lead is planned as well, a second subclavian venipuncture is made, and the atrial lead is placed with the use of the same technique.
10. The leads are connected to the generator, and then pacing and sensing measurements are obtained.
11. If measurements are satisfactory, the lead is screwed in (active fixation) or securely placed among trabeculae (passive fixation). The leads are secured by suture sleeves within the device pocket.
12. The pocket is irrigated with antibiotic solution.
13. The excess lead is coiled and placed into pocket along with the generator.[61]

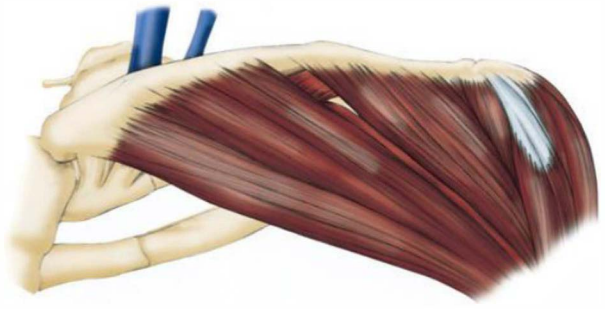


**FIGURE 44-2** Superficial clavicular anatomy. (Reproduced with permission from Calkins H, Ramza BM, Brinker J, et al. Prospective randomized comparison of the safety and effectiveness of placement of endocardial pacemaker and defibrillator leads using the extrathoracic subclavian vein guided by contrast venography versus the cephalic approach. *Pacing Clin Electrophysiol* 2001;24:456–464. Copyright © John Wiley & Sons.)

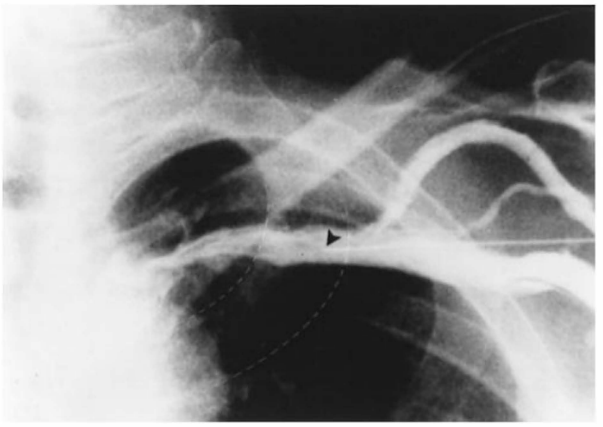


**FIGURE 44-4** Subclavian venography. (Reproduced with permission from Calkins H, Ramza BM, Brinker J, et al. Prospective randomized comparison of the safety and effectiveness of placement of endocardial pacemaker and defibrillator leads using the extrathoracic subclavian vein guided by contrast venography versus the cephalic approach. *Pacing Clin Electrophysiol* 2001;24:456–464. Copyright © John Wiley & Sons.)

In general, if the leads are placed too far laterally, there is a greater risk of arterial puncture, whereas if the placement is too medial, there is increased risk of entrapment by the costoclavicular ligament and/or the subclavius muscle.[62]

If the cephalic approach is used, an oblique incision is made just lateral to the deltopectoral groove at the level of the coracoid process of the scapula. A pocket is created, using standard techniques. After dissection down to the pectoralis fascia and identification of the fat pad, the cephalic vein is dissected free, with proximal and distal control of the vein obtained by using permanent silk sutures. A small venotomy is made in the cephalic vein, which is held open with a vein pick. A standard 50-cm 0.035-in J-tipped guidewire is introduced, and one or two endocardial leads are placed, using standard peel-away sheaths.[61]

## Antibiotic Prophylaxis for Endocardial Leads

Several randomized clinical trials have demonstrated reduced infectious complications following permanent device implantation with empiric periprocedural antibiotic administration.[63] A recent trial by De Oliveiri et al. randomized patients undergoing device implantation in a 1:1 fashion to preimplant antibiotics (1 g cefazolin) or placebo. The study was stopped early due to a five-fold rate of infection in the placebo arm. Predictors of infection included no antibiotics, hematoma, and longer procedure duration.[64] In our institution, 1 g cefazolin (or 1 g clindamycin for patients with penicillin allergy) is given before the procedure. After the procedure, 1 g cefazolin is given every 8 h for a 24-h period. Due to the paucity of clinical data supporting prolonged oral antibiotic therapy, the authors no longer administer additional antibiotics for prophylaxis. There is general consensus that antibiotics should be stopped once the wound is closed or within 24 h of wound closure.

## Temporary Epicardial Leads

Temporary atrial and ventricular epicardial pacing wires are passed superficially through the epicardial surface, with the atrial wires secured superficially with fine polypropylene sutures. The duration of capture with these wires varies, but most start to fail after a week or two. Once they no longer are needed, they generally are extracted, with traction applied to the leads as they emerge from the thorax; this usually causes the suture to break or the lead to pull out from the epicardial surface. This usually does not result in any bleeding.

## Permanent Epicardial Leads

Permanent epicardial leads either screw into the myocardium or are fixed actively in contact with the epicardial surface with deeper polypropylene sutures. As discussed below, placement of permanent epicardial leads requires a small thoracotomy. Any lead can be placed through such a thoracotomy, using standard open surgical techniques. Despite the small size of the thoracotomy, placement of these leads may result in significant postoperative pain, probably because significant force must be applied to spread the ribs during the procedure. There has been increasing experience with placement of epicardial leads using a robotic arm, particularly when a LV lead has to be placed for a biventricular pacing system, as is discussed below. One advantage of this technique is a significant reduction in postoperative pain as a result of the need for only a few small incisions for the arm, camera, and so on.

## Technique for Standard Surgical Placement of Epicardial Leads

Epicardial leads may be placed with the subxiphoid approach or an anterior thoracotomy approach. The subxiphoid approach is preferred in patients without prior cardiac surgery and is performed as follows:

1. With local anesthesia, a vertical midline incision is made below the xiphoid process.
2. The rectus sheath and anterior diaphragm are exposed.
3. The xiphoid process is retracted superiorly or removed, and the subcutaneous fat is dissected.
4. The diaphragmatic portion of the pericardial surface is exposed and opened.
5. Epicardial screw-in leads are attached to the right ventricular free wall.
6. The pericardium is closed around the leads.
7. The generator is placed in the subcutaneous tissue.

The anterior thoracotomy approach often is reserved for patients with prior cardiac surgery and is performed as follows:

1. Access is via the left fifth intercostal space.
2. The anterolateral left ventricle is exposed.
3. The leads are fixed and then tunneled subcutaneously to the pulse generator, which usually is placed in the left upper quadrant of the abdomen.

## Robotic Arm Placement of the Left Ventricular Lead for Biventricular Pacing Systems

In approximately 10 percent of patients referred for a biventricular pacing system, placement of the coronary sinus lead is unsuccessful. In these situations, a surgical LV epicardial lead may be considered. There has been increasing experience with minimally invasive LV epicardial lead placement, using a robotic surgical system such as the da Vinci Robotic Surgical System (Intuitive Surgical, Sunnyvale, CA). In a series of 10 patients[65] in which 19 epicardial leads were placed

(1 patient received only 1 lead), mean robotic operative time for all cases was 83 ± 53 min (range 30–80 min) and was significantly lower in the last five cases (50 ± 16 min) compared with the first five cases (108 ± 54 min). All the patients were alive and well 25 ± 10 weeks after follow-up with significant improvement in NYHA class and LVEF observed. Reported complications included one inadvertent injury to the LV free wall (corrected with robotically placed pledgeted sutures) early in the series. This was attributed to mediastinal shift associated with mechanical ventilation that allowed the LV to move toward the chest well; in subsequent cases, mechanical ventilation was held during lead placement. One patient developed left lower lobe pneumonia 3 days after the procedure. No blood transfusions or reoperations for bleeding were required.

According to the authors, their surgical approach is as follows. The patient is placed in a right lateral decubitus position. In the seventh intercostal space at the posterior axillary line, a camera port is placed. The left and right instrument arms of the robot are passed through ports placed in the ninth and fifth intercostal spaces, respectively. The left chest is insufflated with $CO_2$ to a pressure of 8 to 10 mm Hg, and a 10-mm working port (for the introduction of the lead and sutures) is inserted posterior to the camera port. The pericardium is opened and retracted posterior to the left phrenic nerve. The first and second obtuse marginal (OM) vessels are identified. The pacing lead is introduced through the working port and then secured in place with the robotic arms. (More commonly, a screw-in lead is used, but epicardial steroid-eluting sew-on leads were used in two patients.) In most cases, the lead was placed between the second and third OM vessels, which corresponded to the time of latest ventricular activation as measured by a temporary pacing lead. The pericardium is closed over the permanent leads, which are tunneled to a counterincision in the axilla. After chest tube placement for evacuation of air, the port sites are closed and the patient is repositioned to a supine position and redraped. The leads are then connected to a preexisting device in the pocket or to a new device.[65]

## Left Ventricular Endocardial Pacing

LV pacing via the coronary sinus may be unsuccessful because of anatomical variation, phrenic nerve stimulation, or lead instability. Furthermore, it is estimated that as many as 20 to 30 percent of patients with stable lead placement will have no significant benefit from CRT (nonresponders).[66,67] For these patients alternative methods of pacing the LV endocardium may offer some hope. Several patient series have described techniques for accessing the left ventricle by either a transseptal or a transapical approach.[68–71] In addition to being technically challenging, most agree that an indwelling LV pacing lead poses a stroke risk and requires long-term anticoagulation. Although these techniques are still under development, they remain promising as alternatives for patients with difficult coronary sinus lead placements and/or poor response due to lead location.

# PROGRAMMING PACEMAKERS

## Nomenclature

Pacing modes usually are described with codes consisting of three or four letters. The first letter refers to the chambers paced: A for atrium, V for ventricle, D for both, and O for neither (pacing is turned off). The second letter refers to the chambers sensed, using the same abbreviations employed for pacing (O denotes that sensing is turned off and asynchronous pacing will occur). The third letter refers to the action taken by the pacemaker in response to a sensed signal and may be one of the following: I (inhibit), T (trigger), or D (dual response of inhibiting or triggering for dual-chamber devices). If a fourth letter is used, it is usually R, which refers to rate-responsive pacing. Rate-responsive devices contain a sensor that can adjust the rate in response to temperature, minute ventilation, oxygen saturation, vibration, and other variables. This facilitates appropriate adjustment in heart rate that is based on an individual's physical activity. Dual-chamber pacing often is referred to as physiologic pacing.

## DDD Mode

In the DDD(R) mode, the pacemaker paces and senses both chambers, with the ability to inhibit or trigger a cardiac depolarization in response to a sensed signal. For example, if an intrinsic atrial beat is sensed within a time interval that corresponds to a programmed heart rate threshold (typically 60 bpm), the pacer will not trigger an artificial atrial beat (atrial pacing is inhibited). If the intrinsic atrial rate is slower than the programmed rate, the atrial lead will trigger an artificial atrial depolarization. As the atrial beat travels through the AV conduction system, the ventricular lead will sense whether the impulse has propagated into the ventricle within a preprogrammed time interval (e.g., 200 ms). If the ventricular lead senses intrinsic depolarization, it will not trigger an artificial ventricular beat (i.e., ventricular pacing is inhibited). If after the set time interval the ventricular lead does not sense intrinsic depolarization, it will trigger an artificial ventricular beat. This mode is especially useful for patients with AVB, a need for AV synchrony to maximize cardiac output, or a history of pacemaker syndrome (see "Pacemaker Complications" section below).

## DDI Mode

In the DDI(R) mode, the pacemaker is programmed to pace and sense both the atrium and the ventricle. In response to a sensed signal, the pacemaker will inhibit the output of an artificial depolarization. For example, if the intrinsic atrial rate is slower than the programmed rate, the atrial lead will trigger an artificial atrial depolarization. Unlike the DDD mode, DDI will not trigger a ventricular artificial depolarization on the basis of atrial activity. The only scenario in

which the ventricular lead will trigger an artificial depolarization occurs when the intrinsic ventricular rate is below a programmed threshold.

## VVI Mode

In the VVI(R) mode, the pacemaker paces and senses only the ventricle. If an intrinsic ventricular signal is detected, the ventricular lead will not trigger an artificial ventricular depolarization. This mode is particularly useful for patients with persistent atrial arrhythmias such as atrial fibrillation. Unlike the DDI(R) mode, the VVI(R) mode does not pace the atrium if an intrinsic atrial signal is absent. The disadvantage of this mode compared with DDI(R) is AV dyssynchrony with possible compromise of cardiac output as a result of impaired diastolic filling of the left ventricle if there is a native organized atrial rhythm.

## Mode Switching

Mode switching refers to switching to a mode that is not capable of tracking atrial beats. This is useful in patients with intermittent atrial tachyarrhythmias. Examples are switching from DDDR to DDIR and from DDD to VVI. Although patients with AV nodal ablation for atrial fibrillation may receive greater symptomatic benefit with DDDR and mode switching compared with VVIR,[72] the MOST trial suggested that among patients with SND and paroxysmal atrial fibrillation, DDDR and mode switching do not have any symptomatic benefit.[73]

## Other Modes

In the AAI(R) mode, the pacemaker paces and senses only the atrium. If an intrinsic atrial signal is sensed, the pacemaker will not trigger an atrial depolarization. This mode may be appropriate for patients with SND and intact AV conduction. The disadvantage of this mode is the lack of ventricular pacing if AVB occurs. In a selected group of patients who were screened to find out if they had intact AVN function, the occurrence of clinically significant AV nodal disease was less than 2 percent/year. This mode is used rarely in the United States.

In the DOO mode, both chambers are paced but not sensed. This mode may be used as a temporary mode during surgery to prevent an interaction between the electrocautery and pacemaker sensing. Such an interaction could result in bradycardia or asystole as a result of inappropriate inhibition of ventricular pacing or rapid ventricular pacing resulting from inappropriate electrocautery sensing by the atrial lead with triggered pacing of the ventricle. In the VOO mode, the ventricle is paced but not sensed. The indication is the same as for DOO. Pacemaker-dependent patients who are undergoing cardiac surgery should be switched to one of these modes before surgery.

## Perioperative Device Programming

Both inpatient and outpatient surgical procedures present challenges to health care providers when patients have implantable cardiac rhythm management devices (pacemakers and defibrillators). Most of the concerns center around potential interaction between the device and an electromagnetic field which can cause inability of the device to deliver pacing or shocks, lead–tissue interface damage, changes in pacing behavior, electrical reset to the backup pacing mode, or inappropriate ICD therapies. Electromagnetic interference (EMI) has been reported with MRI scanners, electrosurgery, TENS units, lithotripsy, electroconvulsive therapy, radiation therapy, and radiofrequency ablation among others. Previous guidelines have recommended that all patients with implantable devices have the device interrogated before and after surgery in order to assure proper device function during the perioperative period. In truth, patients with pacemakers who are not pacemaker dependant need no reprogramming. Similarly, pacemaker-dependant patients undergoing procedures involving the groin, lower extremities, or upper extremities distal to the elbow need no reprogramming of the device.[74] At the author's institution, patients undergoing surgery in the head, neck, chest, abdomen, or upper extremities proximal to the elbow are reprogrammed to asynchronous pacing if pacemaker-dependent, and ICD tachycardia therapies are disabled on the day of surgery. Temporary pacing and defibrillation equipment should be readily available. After the operation, the original device settings should be restored with interrogation of the lead parameters. This is particularly important for patients undergoing cardiac surgery during which device leads may become disrupted or dislodged.

# PACEMAKER COMPLICATIONS

## Complications Related to Implantation

Pacemaker complications can be divided into complications associated with implantation, pacemaker infections, subsequent loss of capture, pacemaker syndrome, and pacemaker-mediated tachycardia.

Implantation complications may be related to venous access, the endocardial lead, or the pocket. Complications related to venous access are (1) pneumothorax and hemothorax, (2) incidental arterial puncture, and (3) brachial plexus injury. The incidence of pneumothorax or hemothorax with the subclavian endocardial approach has been estimated to be 1 to 3 percent.[75,76] Complications associated with the endocardial lead are (1) atrial or ventricular perforation, tamponade, and complete heart block, (2) chest wall or diaphragmatic stimulation, and (3) venous thrombosis or endocarditis. Complications associated with the pocket are (1) hematoma (appropriate electrocautery use helps avoid this complication), (2) infection, (3) skin compromise, and (4) generator migration. A complete discussion of pacemaker lead and generator infections follows.

## Pacemaker Lead Infections

Patients may present with systemic infection and pacemaker lead endocarditis or local infection. According to a series involving 52 patients, patients with pacemaker lead endocarditis may present early after pacemaker implantation or late with chronically infected leads. In this series, there was fever in 87 percent, pulmonary involvement in 38 percent, positive blood cultures in 88 percent (most frequently *Staphylococcus* in 94 percent of positive cultures), and abnormalities on the lead by transesophageal echocardiography in 94 percent, often not seen with transthoracic echocardiography.[77]

In patients with local infection, conservative therapy may be considered for very low grade infections or minor skin erosions. In patients who present with a pocket abscess or significant skin erosions, conservative treatment (antibiotics, limited debridement, and irrigation) probably will result in failure.[78,79] Generator removal only and/or partial lead extraction are also likely to result in persistent infection.[78–80]

The decision whether to perform percutaneous or surgical lead extraction for vegetations larger than 1 to 2 cm is controversial. In the series mentioned above, the 10 patients with vegetations larger than 10 mm were referred for surgical lead removal, and 2 of them died of septic complications.[77] Although the authors documented a significant rate of septic pulmonary embolism of 30 percent in the entire cohort,[77] most of those cases were without significant clinical sequelae, and so there is still no strong evidence that surgical extraction is preferable to percutaneous extraction for large vegetations.

## Loss of Capture

Loss of capture may be due to (1) lead dislodgment, (2) lead fracture, (3) a break in lead insulation, and (4) fibrosis at the lead–myocardial interface (increased pacing threshold). Pacemaker interrogation and echocardiography are useful in determining the cause of the loss of capture. For example, lead fracture is associated with high impedance, whereas loss of lead insulation is associated with low impedance.

## Other Complications

Pacemaker syndrome is caused by the absence of AV synchrony during ventricular pacing, usually resulting in atrial contraction against closed AV valves. Since the atrial contraction may result from retrograde conduction of a ventricular pacing impulse, this syndrome may be more common in patients with SND and intact AV conduction than it is in those with AVB. Symptoms of pacemaker syndrome include light-headedness, weakness, flushing, exercise intolerance, and palpitations. The syndrome may be treated by restoration of AV synchrony with DDD pacing.

In pacemaker-mediated tachycardia, the ventricular impulse is conducted retrograde through the AVN to the atria, where it is sensed by the atrial lead in a dual-lead system, with the resulting ventricular-paced beat triggered by the atrial-sensed beat. The acute remedy is to place a magnet over the pacemaker. The long-term remedy is to reprogram the pacemaker to increase the postventricular atrial refractory period (PVARP) or change the mode from DDD to DDI.

# EXTRACTION OF PACING AND DEFIBRILLATING LEADS

## Indications

After the initial implantation of a pacing lead, some degree of thrombosis develops and, on areas that are in contact with the endothelium or endocardium, organizes into fibrosis that may propagate along the lead and over time become increasingly dense and calcified (calcification is more common in very old leads). This fibrotic tissue makes lead removal difficult, necessitating extraction with more sophisticated tools. The most common sites for fibrosis are the venous entry site, the curve into the SVC, and the region from the anode ring to the lead tip.[81]

Experts in complex lead management make the distinction between explanting a lead (simple traction) and lead extraction (use of specialized tools for lead removal).[82] The most common indication for lead extraction is infection, sometimes involving only the pocket but often resulting in vegetations on the pacemaker leads. The most recent class I and class II indications for extraction of chronically implanted leads are listed in Table 44-2.

## Procedural Strategies

Early strategies for lead removal made use of simple traction (later modified to prolong the period of traction with a weight and pulley system) or open chest surgery with cardiopulmonary bypass. As earlier generations of leads were thicker and had greater resistance to loss of integrity during simple traction, this method was often successful. Excessive force, however, created the risk of avulsion of myocardium with resulting tamponade. Experience with surgical extraction of pacemaker leads has been described.[83,84] Generally, surgery is reserved for patients who fail percutaneous extraction and those with large pacemaker lead vegetations, as discussed below.[77]

The need for a safer, faster, and more consistent technique was satisfied by the development of the counter-traction technique that was developed in the late 1980s and evolved during the 1990s.[85,86] This technique employs stylets that are attached to the lead to apply traction while the operator uses a sheath surrounding the lead to free the lead from the fibrotic myocardium and apply countertraction, as shown in Table 44-2.

**TABLE 44-2: Indications for Extraction of Chronically Implanted Transvenous Pacing and Defibrillator Leads[a]**

Class I indications: Complete device and lead removal in patients with:

- Definite CIED system infection, as evidenced by valvular endocarditis, lead endocarditis or sepsis (Level of evidence: B)
- CIED pocket infection as evidenced by pocket abscess, device erosion, skin adherence, or chronic draining sinus without clinically evident involvement of the transvenous portion of the lead system (Level of evidence: B)
- Valvular endocarditis without definite involvement of the lead(s) and/or device (Level of evidence: B)
- Occult gram-positive bacteremia (not contaminant) (Level of evidence: B)
- Life-threatening arrhythmias secondary to a retained lead fragment
- A retained lead, a lead fragment, or extraction hardware that poses an immediate or imminent physical threat to the patient
- Clinically significant thromboembolic events caused by a retained lead or a lead fragment
- Obliteration or occlusion of all usable veins, with the need to implant a new transvenous pacing system
- A lead that interferes with the operation of another implanted device (e.g., pacemaker or defibrillator) or with treatment of malignancy

Class II indications

- Persistent occult Gram-negative bacteremia
- Severe chronic pain, at the device or lead insertion site, that causes significant discomfort for the patient, is not manageable by medical or surgical techniques and for which there is no acceptable alternative
- Ipsilateral venous occlusion preventing access to the venous circulation for required placement of an additional lead, when there is no contraindication for using the contralateral side
- A lead that because of its design or failure may pose a threat to the patient, though the threat is not immediate or imminent if the lead is left in place
- An abandoned functional lead that poses a risk of interference with the operation of the active CIED system
- Leads that are functional but not being used (i.e., RV pacing lead after upgrade to ICD)
- Patients who require specific imaging techniques (e.g., MRI) that cannot be imaged due to the presence of the CIED system for which there is no other available imaging alternative for the diagnosis
- In patients if a CIED implantation would require more than four leads on one side or more than five leads through the SVC

CIED, cardiovascular implantable electronic devices.

[a]Class I indications are those for which there is general agreement that leads should be removed. Class II indications are those for which leads often are removed but there is some divergence of opinion with respect to the benefit versus risk of removal.

Reproduced with permission from Wilkoff B, Love C, Byrd C, et al. Transvenous lead extraction: Heart Rhythm Society expert consensus on facilities, training, indications, and patient management: This document was endorsed by the American Heart Association (AHA). *Heart Rhythm* 2009;6(7):1085–1104.

The extraction procedure is as follows. The generator is removed from the pocket, and the fibrous tissue is separated from the leads down to the subclavian vein, using electrocautery and/or sharp dissection. If a brief trial of gentle traction fails, the countertraction tools are employed. A special locking stylet is chosen according to the size of the lead and advanced as far as possible along the lead and then fixed to the inner coil. A suture is placed tightly around the lead in an attempt to maintain the integrity of the lead during the extraction process. Several sheath options can be employed at this point including mechanical, telescoping, laser, electrosurgical (RF), and a rotating threaded tip sheath. Although traction is applied to the lead, the sheath is advanced along the lead to lyse fibrous attachments. The sheath is generally advanced to within 1 to 2 cm of the electrode tip. As shown in Fig. 44-5, the lead and myocardium are pulled up to the sheath for countertraction, and then continued traction results in release of the lead tip.

Regardless of the tools employed, careful patient selection according to guidelines and procedural preparation are critical to good outcomes. In addition to the primary operator and a scrubbed assistant, an in-house cardiac surgeon should be identified as well as anesthesia backup if the case is not being done under general anesthesia. At the author's institution, all leads older than 6 months are removed in a hybrid operating room with fluoroscopy under general anesthesia. A transesophageal echo probe is passed and remains in place for the duration of the case for real-time monitoring of intracardiac structures and the pericardial space. The radial artery is cannulated for hemodynamic monitoring and venous sheath is placed in the femoral vein for quick conversion to a femoral work station should that become necessary. At a minimum, it is recommended that primary operators will have extracted 40 leads under the supervision of someone who has extracted at least 75 leads. An additional 20 leads/year should be extracted to maintain proficiency.[82]

The overall complete extraction success rate for conventional countertraction in prior series has been reported to be between 87 and 93 percent, with a major complication rate between 1.4 and 2.5 percent.[87,88] Conversion to a femoral approach sometimes is required because of failure with the subclavian approach. The femoral approach allows the operator to grasp the lead and pull it down from the subclavian implant site and then retrieve it by using countertraction from below with a specially designed sheath. The need for a femoral approach occurs about 5 to 10 percent of the time and increases the overall success rate. More recent data collected with a spectrum of extraction techniques suggest

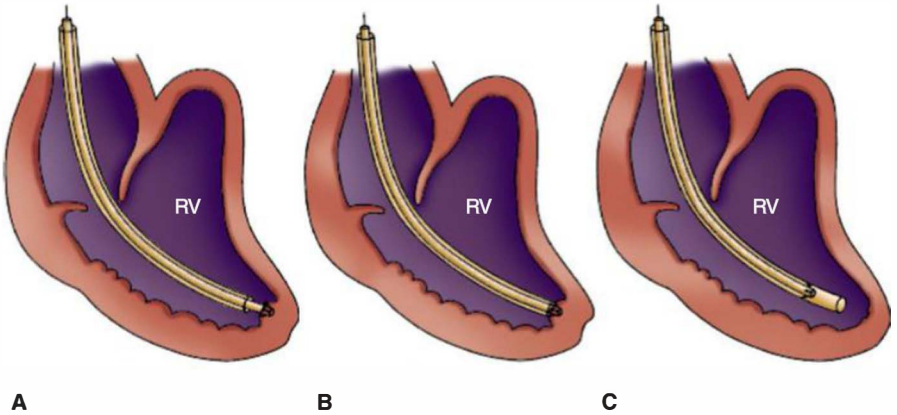



**FIGURE 44-5** Countertraction sequence. **A**. The sheath is advanced to within 2 cm of the lead tip. **B**. The lead and myocardium are pulled up to the sheath to apply countertraction. **C**. The tip releases, and the myocardium falls away. (Reproduced with permission from Love CJ. Current concepts in extraction of transvenous pacing and ICD leads. *Cardiol Clin* 2000;18:193–217. Copyright © Elsevier.)

that major complications remain less than 2 percent in the hands of skilled operators.

The risk of failed extraction increases significantly with increasing age of the lead.[88] Potential major complications of the procedure include death, cardiac tamponade, pneumothorax, hemothorax, pulmonary embolism, arteriovenous fistulas, and stroke.

An excimer laser sheath composed of thin inner and outer polymer walls between which a single layer of optical fibers is embedded is commonly employed for extraction. Proximally, the optical fibers are attached to an excimer laser generator. Distally, pulses of light with wavelengths of 308 nm are delivered to the tissue. Since the penetration of this wavelength of light in vascular tissue is approximately 100 μm, only the fibrous tissue immediately surrounding the sheath tip is destroyed, facilitating lead extraction. The PLEXES (Pacing Lead Extraction with the Excimer Sheath) trial randomized 301 patients with 465 chronic leads to extraction via a subclavian approach with a conventional sheath or the excimer sheath. Complete removal was achieved in 94 percent of the laser group but in only 64 percent of the conventional group. Rather than converting to a femoral approach, leads that failed with the conventional approach were removed with the laser sheath, with a success rate of 88 percent. Significant complications were encountered in less than 2 percent of the patients, but none was attributed directly to the use of the laser.[89] The recent LEXICON study was a multicenter observational trial of 1449 patients undergoing laser-assisted device extraction. Use of the laser was associated with a 97.7 percent clinical success rate and major adverse events in 1.4 percent, including four deaths (0.28 percent), compared with a 2.5 percent major complication rate and an 0.6 percent death rate in a registry involving the conventional approach.[90,91] The Evolution™ mechanical dilator sheath is a useful alternative to the laser sheath with successful extraction reported in over 80 percent of patients.[92] This tool has proven particularly useful in regions of heavy vascular and lead fibrosis or calcification.

## Other Considerations

Nonfunctional leads do not require routine extraction. In most cases, the leads may be abandoned and new leads can be inserted ipsilaterally. A special case is that of Accufix (Telectronics) and Encor™ (Telectronics) atrial leads, which have been implicated as a cause of death in 6 of over 30,000 patients as a result of fracture of the small retention wire used to form the J shape. This family of leads was withdrawn from the market in 1994; however, some 8000 patients still have these leads implanted. Fracture of this retention wire may work its way through the insulation and perforate the heart. Although some physicians initially elected to remove the leads, the incidence of death (about 0.5 percent) from this procedure was found to be higher than that resulting from the lead itself. On the basis of those findings, physicians were advised to manage patients more conservatively by following them with serial fluoroscopy, with consideration of extraction only for certain indications that were based on patient age, duration of implant, and fracture class of the retention wire.[93] In cases of perforation of the insulation by retention wire (class III fracture), it may be possible to snare and selectively retrieve the fractured wire fragment by using percutaneous techniques. Similarly, the Sprint Fidelis is a Medtronic ICD lead implanted in 286,000 patients worldwide. Due to its high rate of failure and predilection for fracture, this lead was voluntarily withdrawn. Failure can involve the pace/sense portion and/or the shocking coils. Pace/sense conductor failures can cause oversensing resulting in inappropriate shocks or pacing failure due to high impendence. Fracture of the high-voltage electrode can cause failure to deliver shocks. Current recommendations include regular device follow-up

and a software patch for longitudinal monitoring. However, a 2008 study showed that impendence monitoring failed to prevent 2/3 of inappropriate shocks.[94]

For occlusion of the subclavian vein, conservative management, including short-term anticoagulation, is often adequate, as these patients generally develop venous collaterals. For patients with SVC syndrome in whom dilatation and stenting is planned, extraction of the lead should be considered.[94,95] The occurrence of pulmonary emboli generally does not mandate lead extraction unless the emboli are clinically significant or recurrent despite appropriate anticoagulation.[93]

Pacing leads implanted inadvertently in the left ventricle should be removed immediately. Chronic LV leads should be treated with anticoagulation, with surgical extraction reserved for recurrent cardioembolic stroke despite anticoagulation. Percutaneous extraction is less desirable because of the potential embolization associated with passing the sheaths over the leads and rarely is performed. In regard to tricuspid regurgitation, lead extraction rarely has been of any benefit and can worsen the condition by damaging the valve.

Defibrillator leads can be extracted with the same percutaneous techniques described for pacing leads, with similar success. Coronary venous leads used for biventricular pacing have been removed with remarkably little difficulty, although there is little experience to date with the Medtronic StarFix™ active fixation coronary sinus lead.

# DEFIBRILLATORS

## General Considerations

ICDs were introduced in the 1980s as a means of rescuing patients from life-threatening ventricular tachyarrhythmias. The detection of VT is based primarily on the ventricular rate rather than the width of the QRS complex on the surface ECG. When the ventricular rate exceeds a programmed threshold, the device delivers a shock to restore the normal rhythm. Current ICD systems may consist of either one or two leads, with the second configuration designed to allow dual-chamber pacing if necessary. The procedure for implanting an ICD system is similar to that for implanting a pacemaker. With the patient under conscious sedation and local anesthesia, a cardiologist or surgeon inserts a pulse generator subcutaneously and inferior to the left clavicle. The pulse generator is connected to the lead(s) in the RV (and the right atrium with two-lead systems). When the ICD fires, the circuit consists of a ventricular coil as one pole and the pulse generator and/or another coil in the SVC/right atrium as the other pole. The pulse generator typically is positioned on the patient's left side, allowing the maximum amount of current to traverse the heart. Of note, ICD leads, like pacemaker leads, may be extracted, but the extraction procedure is more complex because of the ingrowth of tissue into the shock coils. This may be mitigated by the introduction of Gore-Tex-coated coils.

## Modes of ICD Therapy

The ICD classifies a rhythm on the basis of the ventricular rate. For example, most ICDs are programmed to have one to three zones of tachytherapy plus bradycardia pacing. The device delivers the programmed therapy on the basis of the heart rate it detects. Available therapies include bradycardia pacing, antitachycardia pacing (ATP), and shock delivery. In ATP, the device initiates a short burst of rapid ventricular pacing in an effort to interrupt the reentrant tachycardia by creating a critical zone of conduction within the reentrant circuit that is refractory to additional ventricular activation. The shock may be delivered in the form of low-energy cardioversion or defibrillation. Most ICDs are capable of delivering 30 J or more to terminate unstable VT and ventricular fibrillation (VF).

## Interpreting an ICD Interrogation

All ICDs can be interrogated noninvasively to obtain the program that describes what the device will do for a given abnormal heart rate and/or to verify that a reported shock was indeed a shock and was delivered appropriately for VT or VF. An ICD interrogation slip is shown in Figure 44-6. Intracardiac electrograms are depicted. From top to bottom, these are the near-field atrial electrogram, the near-field ventricular electrogram, and the far-field electrogram, which represents a closer approximation to the surface ECG. Inspection of this episode shows initial atrial and ventricular depolarizations in a sequence consistent with sinus rhythm. A premature ventricular depolarization follows and initiates VF at a cycle length less than 200 ms. During the episode of VF, the activity depicted in the near-field atrial electrogram is unrelated to that in the near-field ventricular electrogram, consistent with VF. The VF is treated successfully with a 21-J biphasic shock. After the shock, the ensuing bradycardia prompts the device to initiate post-shock AV pacing, which is manifested as a wide-complex ventricular rhythm on the far-field electrogram. Interrogation of the device after a shock is important to document appropriate sensing and treatment of the ventricular arrhythmia.

## Major Indications for ICD Implantation

The major class I indications for ICD implantation as reported by the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities are listed below[4]:

1. Survivors of cardiac arrest caused by VT or VF that has an irreversible cause (class I): A mortality benefit has been demonstrated in the Antiarrhythmics versus Implantable Defibrillator (AVID) trial.[96]
2. Spontaneous sustained VT in the presence of structural heart disease (class I): A mortality benefit for this indication also has been demonstrated in the AVID trial.[96]

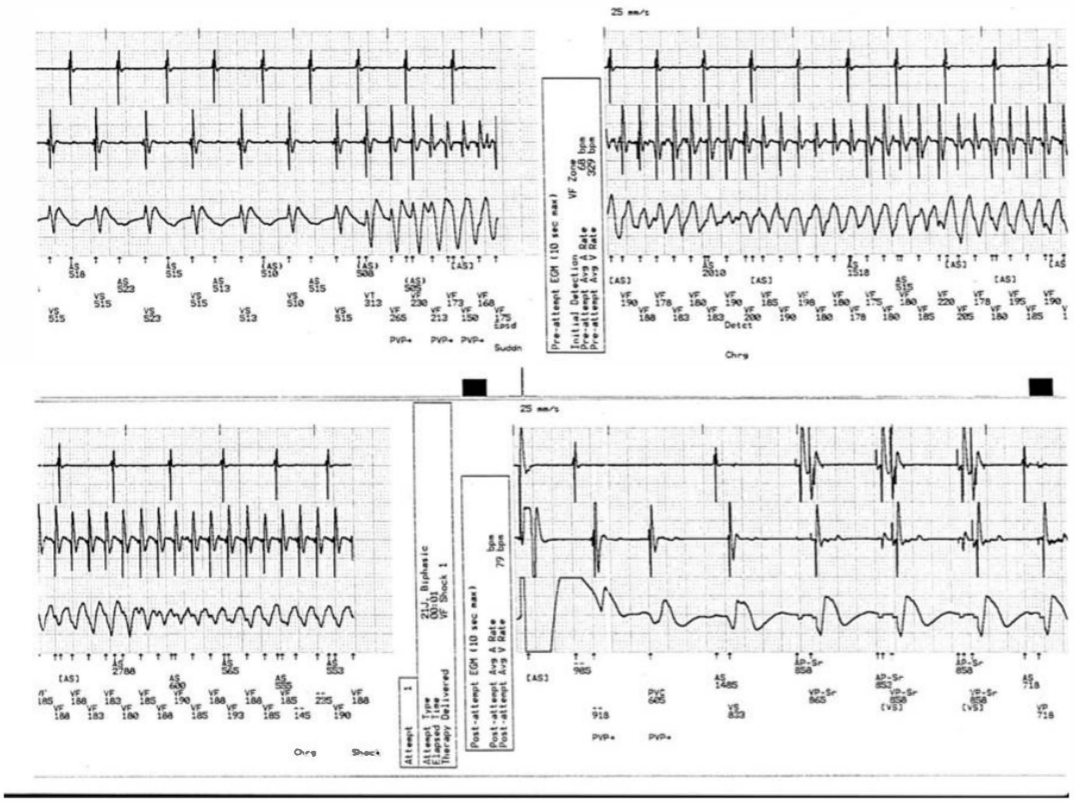


**FIGURE 44-6** ICD interrogation slip. In order from top to bottom, atrial near-field electrogram, ventricular near-field electrogram, and far-field electrogram are shown. Sinus rhythm is followed by a premature ventricular contraction initiating VF (cycle length <200 ms), which resolves with a 21-J biphasic shock and is followed by postshock ventricular pacing. Note that during VF, AV dissociation is present.

3. ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study.[97]
4. ICD therapy is indicated in patients with LVEF less than 35 percent due to prior myocardial infarction who are at least 40 days post-myocardial infarction and are in NYHA functional class II or III.
5. ICD therapy is indicated in patients with nonischemic dilated cardiomyopathy who have an LVEF less than or equal to 35 percent and who are in NYHA functional class II or III. This recommendation is due to the landmark Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) which showed a 23 percent reduction in mortality in nonischemic heart failure patients (NYHA class II/III, EF ≤35 percent) who received a prophylactic ICD versus placebo.[51] Of note, the SCD-HeFT trial showed a similar magnitude of survival benefit whether the cardiomyopathy was of ischemic or nonischemic etiology.[50,51]
6. ICD therapy is indicated in patients with LV dysfunction due to prior myocardial infarction who are at least 40 days postmyocardial infarction, have an LVEF less than 30 percent, and are in NYHA functional class I.[52] This indication is based on the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II), in which patients with a prior myocardial infarction and an EF less than or equal to 30 percent who received an ICD had 31 percent lower mortality after 20 months of follow-up than did those given conventional therapy.[98] An important task that lies ahead is to find more specific ways to risk stratify this large population, as the economic burden of having all patients in this group receive ICDs would be quite large.
7. ICD therapy is indicated in patients with nonsustained VT due to prior myocardial infarction, LVEF less than 40 percent, and inducible VF or sustained VT at electrophysiological study.[99]

## Defibrillators in Cardiac Surgery Patients

When considering therapy with an ICD for patients referred for cardiac surgery or with recent cardiac surgery, the following points should be considered. First, revascularization

constitutes excellent antiarrhythmic therapy. The CABG-Patch trial[100] randomized 900 patients scheduled for CABG, EF equal to or less than 35 percent, and an abnormal signal-averaged ECG (SAECG) indicates an increased arrhythmia risk. Even with an overall 42-month mortality rate of 24 percent as would be expected for higher risk patients, there was no significant decrease in mortality associated with ICDs after 32 ± 6 months of follow-up. Many trials showing benefit for ICDs, such as the AVID,[96] MADIT-I,[99] and MADIT-II[98] trials, excluded patients referred for CABG and those with recent CABG. For example, MADIT-II excluded patients who had undergone CABG within 3 months.[98] As a result, patients with EF equal to or less than 30 percent shortly after CABG do not meet the criteria for an ICD on the basis of the MADIT-II study. Of note, a post hoc analysis of 281 patients excluded from the AVID trial because they were referred for CABG showed a trend for ICD benefit compared with antiarrhythmic drugs.[96] However, these results are difficult to interpret in light of the post hoc analysis, nonrandomized patients, and lack of statistical significance.

In regard to ICDs in early postsurgical patients, it is important to note that an ICD does not constitute acute therapy for sustained ventricular arrhythmias. On the contrary, ICDs are meant to be a mode of chronic primary or secondary prevention of sudden death associated with ventricular arrhythmias. If a postsurgical patient is having frequent sustained ventricular arrhythmias, that patient should be rendered arrhythmia free with medical therapy first. The drug of choice in patients with recent CABG is usually amiodarone if there are no contraindications, although other antiarrhythmic drugs may be considered. If amiodarone is chosen and the patient has breakthrough ventricular arrhythmias, additional IV loading doses of amiodarone are frequently effective. In a postsurgical patient who already has an ICD, there still may be a need for external defibrillation. Since most devices assess the need for therapy on the basis of heart rate, a patient may have symptomatic VT at a rate that is below the threshold for initiating automated therapy (particularly if the patient has been on an antiarrhythmic drug such as amiodarone). In patients referred for both cardiac surgery and an ICD, the ICD should be implanted after the surgery due to the potential for lead displacement during surgery.

Finally, patients with a history of cardiac surgery may be referred at some point for CRT (discussed earlier) for class III or IV heart failure associated with a dilated cardiomyopathy (EF less than 35 percent) and intraventricular conduction delay. Results from the COMPANION trial demonstrated a 43 percent reduction in mortality compared with optimal medical therapy in patients who met all the criteria and received a combined defibrillator and biventricular pacemaker.[47] As a result, such patients should be considered for an ICD in addition to CRT. Patients who meet the implant criteria for a CRT device and are referred for cardiac surgery may be considered for LV lead implantation to obviate the later potential need for transvenous placement via the coronary sinus.

## DISCLAIMER

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## PACEMAKER AND DEFIBRILLATOR THERAPY IN CARDIAC SURGERY PATIENTS BOARD REVIEW QUESTIONS (CHAPTER 44)

1. Which of the following principles apply to the SA node and AVN?
   A. They are fast-response tissues with a baseline membrane potential of −90 mV.
   B. The SA node is a discrete endocardial structure that is easily damaged.
   C. In most individuals the majority of the blood supply to the SA and AVNs comes from the left circumflex artery.
   D. Depolarization of the SA and AVNs depends largely on L-type calcium currents.
   E. The conduction velocity of the SA and AVNs is much faster than the infranodal conduction system.

2. Which of the following is *not* a class I indication for a PPM?
   A. Sinus node dysfunction with symptomatic bradycardia.
   B. AVB in symptom-free patients in AF with pauses >5 seconds.
   C. Asymptomatic LAFB and first degree AVB.
   D. Third degree AVB that results from required drug therapy for medical conditions.
   E. Alternating LBBB and LBBB.

3. All of the following statements about device programming are true *except*:
   A. DDI mode will trigger a ventricular depolarization on the basis of atrial activity.
   B. Patients with pacemakers who are pacemaker dependant should be programmed asynchronously before surgery.
   C. Potential interaction between the device and an electromagnetic field include inability of the device to deliver pacing or shocks, lead-tissue interface damage, changes in pacing behavior, electrical reset to the backup pacing mode, or inappropriate implantable cardioverter-defibrillator (ICD) therapies.
   D. Electromagnetic interference has been reported with TENS units.
   E. Mode switching usually occurs in the setting of atrial tachyarrhythmias and avoids ventricular tracking of rapid atrial beats.

4. A 47-year-old man with an ischemic cardiomyopathy and prior dual chamber ICD implantation presents with a device erosion. The device was implanted 16 months prior to presentation and he is not pacemaker dependant. According to the AHA/HRS Consensus document, proper management includes:
   A. Extraction of the generator and capping the leads followed by a trial of prolonged antibiotics.
   B. Extraction of the generator and both leads in the EP lab with immediate reimplantation of a device on the contralateral side.
   C. Extraction of the generator and both leads in the operating room with cardiac surgery backup readily available.
   D. Wound washout and revision with plastic surgery and prolonged antibiotics.
   E. Generator and lead extraction in the operating room with cardiac surgery backup followed by placement of an epicardial defibrillator patch.

5. A 65-year-old woman with a non-ischemic cardiomyopathy and EF 25 percent presents to your office complaining of dyspnea with mild activity, fluid retention, and weight gain despite optimal medical management. Her ECG shows sinus rhythm with a LBBB. Which of the following statements outlines the best course of action?
   A. Refer her for a single chamber ICD and consider upgrade to a CRT device based upon the results of a dyssynchrony echocardiogram.
   B. Refer her for a CRT device without defibrillator therapy.
   C. Refer her for a CRT-D device with a coronary sinus lead.
   D. Refer her for a CRT-D device with a robotically placed epicardial LV pacing system.
   E. Refer her for an LV assist device.

## ANSWERS

1. **Answer: D.** The baseline membrane potential of fast-response tissue is −90 mV and the peak is +20 (Fig. 39-1). The depolarization of fast-response tissues such as the atria, the bundle of His, bundle branches, and Purkinje fibers is due to an inward sodium current, whereas repolarization of those tissues is due primarily to outward potassium currents. In slow-response tissues such as the sinus node and the AVN, the baseline is about −70 mV and depolarization depends primarily on the L-type calcium current. The SA node is a diffuse and robust subepicardial structure that is surrounded by connective tissue. In most individuals, the majority of the blood supply to the SA and AVNs is from the RCA.
2. **Answer: C.** PPM implantation is not indicated for fascicular block with first degree AVB without symptoms (class III indication). All of the other choices are class I indications.
3. **Answer: A.** The DDI mode is dual-chamber, dual-sensed inhibition of depolarization. Unlike the DDD mode, DDI will not trigger a ventricular artificial depolarization on the basis of atrial activity. The only scenario in which the ventricular lead will trigger an artificial depolarization occurs when the intrinsic ventricular rate is below a programmed threshold.
4. **Answer: C.** Device erosion is a class I indication for complete generator and lead removal. Leads older than a year should be removed in the operating room with cardiac surgery backup. In a patient that is not pacemaker dependant, a course of antibiotics should be completed without additional hardware in place before reimplantation on the contralateral side.
5. **Answer: C.** This patient meets SCD-HeFT criteria for implantation of a primary prevention ICD. Based upon the results of the COMPANION trial, the FDA has approved the use of devices that combine an ICD and a biventricular pacemaker in patients who meet criteria for CRT.

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# Surgical Treatment of Chronic Pulmonary Thromboembolic Disease

*Michael M. Madani*
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## KEY CONCEPTS

- Epidemiology
  - The precise incidence of pulmonary embolism (PE) is unknown; it is estimated to be in the range of 1 to 3 in 1000 individuals. Approximately 75 percent of autopsy-proven PEs are not detected clinically. PE is particularly common in hospitalized elderly patients.
- Pathophysiology
  - PE is usually an embolic manifestation of deep venous thrombosis (DVT), which is caused by venous stasis, vein wall injury, and hypercoagulopathy.
  - Other etiologies include malignancy, chronic indwelling central venous catheters, pacemaker leads, and spontaneous thromboses.
  - Emboli become lodged in the pulmonary artery bed and lead to pulmonary vascular hypertension by several proposed processes: redirected pulmonary blood flow, neurovascular perturbation, and hormonal changes.
- Clinical features
  - Chronic thromboembolic pulmonary hypertension (CTEPH) presents insidiously with vague symptomatology. Suspicion should be raised when signs and symptoms for DVT (e.g., leg swelling, lower extremity venous stasis changes, chest pain, hemoptysis) are encountered.
  - The most common symptoms associated with pulmonary hypertension are exertional dyspnea, presyncope/syncope, and nonspecific chest pain or pressure.
  - The physical signs of CTEPH are related to right heart failure, including a large A wave progressing to a predominant V wave component in the jugular venous pulse. The $S_2$ sound often is narrowly split, and $P_2$ is accentuated; a sharp systolic ejection click may be heard over the pulmonary artery in the second intercostal space. Hypoxia/cyanosis and a right ventricular heave are observed with advanced disease.
- Diagnostics
  - Characteristic findings on plain chest radiography are central pulmonary vascular enlargement, vascular pruning, and right ventricular enlargement.
  - Electrocardiography may demonstrate criteria for right ventricular hypertrophy, including right axis deviation and a dominant R wave in $V_1$.
  - Pulmonary function tests usually reveal minimal changes in lung volume and ventilation with normal or slightly restricted mechanics; the diffusing capacity of the lung for carbon monoxide (DLCO) often is reduced and is the only abnormality on this test.
  - The ventilation perfusion lung scan is essential for diagnosis; an entirely normal scan excludes the diagnosis, whereas most patients with CTEPH demonstrate one or more segmental or larger perfusion defects in otherwise normal lung regions. The magnitude of perfusion defects in chronic thromboembolic disease often underestimates the actual degree of vascular obstruction. A positive scan should prompt a right heart catheterization and pulmonary angiography.
  - High-resolution computed tomography is being used more frequently in the diagnosis of pulmonary thromboembolic disease. However, the gold standard for diagnosis of CTEPH is conventional biplane pulmonary angiography.
- Treatment
  - Medical therapy for CTEPH is limited and generally palliative. New forms of drug therapies are now available for treatment of pulmonary hypertension; however, their benefit in patients with CTEPH is very

limited. Chronic anticoagulation is the mainstay of medical treatment in these patients.
  - Surgical removal of chronic thromboembolic material is the only curative option for patients with CTEPH.
- Outcomes and prognosis
  - Pulmonary endarterectomy (PEA) is a proven procedure for the treatment of CTEPH with excellent long-term results. A 30-year experience at the University of California, San Diego (UCSD) Medical Center indicated an overall operative mortality of 8 percent. This has declined to a current rate of about 2.2 percent.
  - A complication specific to PEA is a reperfusion pulmonary edema that appears to be related to reperfusion of endarterectomized regions.
  - In most treated patients, a significant reduction in pulmonary pressures and pulmonary vascular resistance and a significant increase in pulmonary blood flow and cardiac output are observed immediately and sustained. One year postoperatively, 95 percent of treated patients have improved from New York Heart Association functional class III or IV to functional class I or II.

## INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a common condition that is severely under diagnosed. The disease is caused by chronic obstruction of the pulmonary vasculature as a result of longstanding pulmonary thromboembolism. Once the diagnosis is made, there is only one curative option: surgical removal. Medical therapy remains palliative at best, and lung transplantation for this condition is outdated. Pulmonary endarterectomy (PEA) is a curative procedure for the treatment of CTEPH with excellent short- and long-term outcomes, but unfortunately it remains an uncommonly performed operation.

Acute pulmonary embolism (PE) is one of the more common cardiovascular diseases affecting Americans. Despite clinical and statistical evidence of progression of the disease in survivors, the majority of patients continue to be misdiagnosed. Perhaps one contributing issue is the fact that there are no specific signs and symptoms associated with this condition. Furthermore, most patients do not have a definitive history of deep vein thrombosis (DVT) or acute PE. The vague nature of symptoms, including dyspnea on exertion and occasional angina-like chest pains, coupled with lack of awareness among common practitioners, makes the diagnosis quite difficult; unfortunately these patients often progress to severe degrees of pulmonary hypertension and right heart failure before a diagnosis is established and treatment strategy is sought.

The precise incidence of PE remains unknown, but there are some legitimate estimates. It is estimated that acute PE occurs in about 1 person out of 1000,[1,2] which puts the annual incidence of acute PE at about 300,000 in the United States alone. The majority of patients with acute PE will resolve their clots with conventional treatments. However, it is estimated that about 3.8 percent of affected patients will go on to develop chronic pulmonary hypertension by 2 years.[1] This is, however, a low estimate, since in 70 to 80 percent of patients where the primary cause of death was PE, a premortem diagnosis was unsuspected.[3,4] The disease is particularly common in hospitalized elderly patients. Of hospitalized patients who develop PE, 12 to 21 percent die in the hospital, and another 24 to 39 percent die within 12 months.[5–7] Another unrecognized subgroup of patients comprises those with intracardiac catheters, shunts, or leads. The true incidence of chronic thromboembolic disease in these patients is unknown, but clearly these devices carry an inherent risk which is usually overlooked by the implanting physicians.

The mainstay of treatment of patients with DVT and acute PE is medical management. There are few indications for surgical intervention in the acute setting and they are specific to patients who have suffered a massive embolus that causes life-threatening acute right heart failure and severe hemodynamic compromise. The presence of large embolic material in the right atrium or right ventricle evidenced by echocardiography in the setting of severe right heart failure and hemodynamic compromise is another instance where surgery would be indicated. These indications are, however, few and far between. In contrast, in the chronic form of this disease, the only treatment is the surgical removal of the thromboembolic material with PEA. The role of medical therapy in these patients remains unclear and may be limited to patients with residual pulmonary hypertension after endarterectomy. For the most part, medical management is only palliative and does not address the obstructive nature of this disease. The only other potential surgical cure is transplantation. However, lung or heart–lung transplantation as a surgical cure for this condition is an outdated form of therapy and should be considered an inappropriate use of resources that yields less than satisfactory results.

The prognosis for patients with pulmonary hypertension is poor, and it is worse for those who do not have intracardiac shunts. Thus, patients with primary pulmonary hypertension and those with pulmonary hypertension secondary to PE fall into a higher risk category than those with Eisenmenger syndrome, and have a higher mortality rate. In fact, once the mean pulmonary arterial pressure in patients with thromboembolic disease reaches 50 mm Hg or more, the 3-year mortality approaches 90 percent.

Regardless of the exact incidence or the circumstances, it is clear that acute embolism and its chronic relation, fixed chronic thromboembolic occlusive disease, are both much more common than generally appreciated and are

significantly under diagnosed. Calculations extrapolated from mortality rates and the random incidence of major thrombotic occlusion found at autopsy would support a postulate that more than 100,000 people in the United States currently have pulmonary hypertension that could be relieved by operation. The procedure appears to be permanently curative, but fewer than 200 of these are performed annually; most of them at the authors' center, the University of California, San Diego (UCSD). This chapter provides an overview of the pathophysiology of this disease and outlines the surgical management as it is performed at UCSD.

## PATHOPHYSIOLOGY

In 1856 Rudolf Virchow made the association between DVT and PE and suggested that the causes of DVT were related to venous stasis, vein wall injury, and hypercoagulopathy. This triad of etiologic factors remains relevant today and is supported by an ever-growing body of evidence. Although a majority of individuals with chronic pulmonary thromboembolic disease are unaware of a precedent thromboembolic event and give no history of DVT, the foundation of most cases of unresolved PE is based on acute embolic episodes. Why some patients have unresolved emboli is not certain, but a variety of factors must play a role, alone or in combination.

In some cases, the volume of acute embolic material may overwhelm the lytic mechanisms. In other cases, total occlusion of a major arterial branch may prevent lytic material from reaching, and therefore dissolving, the embolus completely. Recurring emboli may not be able to be resolved. The embolic material may be made of substances that cannot be resolved by normal mechanisms (already well-organized fibrous thrombus, fat, or tumor). In some patients, the lytic mechanisms themselves may be abnormal, and other patients may have a propensity for thrombus formation or a hypercoagulable state.

Synchronized preservation of the fluidity of blood and the integrity of the vascular system entails a balance between blood pro- and anticoagulants. Some patients have deficiencies in natural anticoagulants. Three uncommon familial deficiencies associated with venous thrombosis are deficiencies in antithrombin, protein C, and protein S. Antithrombin is a natural plasma protease that inhibits thrombin after it is formed and, to a lesser extent, before it is formed. Antithrombin is also the cofactor that is accelerated 1000-fold by heparin. Protein C is a potent inhibitor of factor V and platelet-bound factor VII and requires protein S as a cofactor for anticoagulant activity. Both protein C and S are vitamin K–dependent zymogens that are activated by thrombin and accelerated by thrombomodulin produced by endothelial cells.

A much more common coagulation deficiency that results from a mutation of factor V (factor V Leiden) that prevents its degradation by protein C has been described and is present in approximately 6 to 7 percent of study populations of Swedish and North American males.[8–11] Both the homozygous and heterozygous mutants are strongly associated with venous thrombosis and PE but are not associated with stroke, myocardial infarction, and other manifestations of arterial thrombosis.[11,12]

The presence of the lupus anticoagulant, which is an acquired immunoglobulin G (IgG) or IgM antibody against prothrombinase, increases the likelihood of venous thrombosis.[12] The disease may be associated with lupus-like syndromes, immunosuppression, or the intake of specific drugs, such as procainamide.

In most cases, regardless of the etiology of the embolus, after the clot becomes wedged in the pulmonary artery, one of two processes occurs[13]: (1) organization of the clot proceeding to canalization, producing multiple small endothelialized channels separated by fibrous septa (i.e., bands and webs) or (2) complete fibrous organization of the fibrin clot, leading to a solid mass of dense fibrous connective tissue totally obstructing the arterial lumen.

In addition to the usual pattern of venous thrombosis and subsequent embolization, usually from the legs or pelvis, there are other special circumstances that may lead to PEs. Chronic indwelling central venous catheters and pacemaker leads sometimes are associated with PEs. Rare causes include tumor emboli, and tumor fragments from stomach, breast, and kidney malignancies, which have been demonstrated to cause chronic pulmonary arterial occlusion. Right atrial myxomas may also fragment and embolize.

In addition to the embolic material, a propensity for thrombosis or a hypercoaguable state may result in spontaneous thrombosis within the pulmonary vascular bed, or encourage proximal propagation of thrombus after an embolus. Whatever the predisposing factors to residual thrombus within the vessels, the final genesis of the resultant pulmonary vascular hypertension may be complex. With the passage of time, the increased pressure and flow as a result of redirected pulmonary blood flow in the previously normal pulmonary vascular bed can create a vasculopathy in the small precapillary blood vessels similar to that seen with Eisenmenger syndrome.

Factors other than the simple hemodynamic consequences of redirected blood flow are probably also involved in this process. For example, after a pneumonectomy, 100 percent of the right ventricular output flows to one lung, yet little increase in pulmonary pressure occurs, even with follow-up to 11 years.[14] In patients with thromboembolic disease, however, one frequently detects pulmonary hypertension even when less than 50 percent of the vascular bed is occluded by thrombus. It thus appears that sympathetic neural connections, hormonal changes, or both might initiate pulmonary hypertension in the initially unaffected pulmonary vascular bed. This process can occur when the initial occlusion is in the same lung or the contralateral lung.

Regardless of the etiology, the advancement of pulmonary hypertension as a consequence of changes in the previously unobstructed bed is serious, since this process may lead to an inoperable condition. Thus, with accumulating experience in patients with thromboembolic pulmonary hypertension,

the authors increasingly have been inclined toward early operation so as to avoid these changes.

## CLINICAL FEATURES

CTEPH is severely underdiagnosed because there are no specific clinical features. Although the majority of pulmonary thromboembolic material originates from a DVT, more than half of the patients with CTEPH do not have a history of DVT or PE. The clinical history may therefore not be helpful, making the diagnosis even more difficult. Nevertheless, during clinical evaluation, predisposing factors for DVT should be sought, as should a history of leg swelling, chest pain, hemoptysis, or any symptom to indicate episodes of PE.

The diagnosis in most patients may be quite difficult since the onset of the disease is insidious. The most frequent symptom coupled with thromboembolic pulmonary hypertension, as with all other sources of pulmonary hypertension, is exertional dyspnea. This dyspnea is out of proportion to any anomalies found on clinical examination. Similar to complaints of easy fatigability, dyspnea that initially occurs only with exertion is often attributed to anxiety or being "out of shape." Syncope or presyncope (light-headedness during exertion) is another frequent symptom in pulmonary hypertension. Generally, it occurs in patients with more advanced disease and higher pulmonary arterial pressures.

Another relatively common complaint with CTEPH is nonspecific chest pain or chest pressure. These occur in approximately 50 percent of patients with more severe pulmonary hypertension. Hemoptysis can occur in all forms of pulmonary hypertension including CTEPH. It probably results from abnormally dilated vessels distended by increased intravascular pressures. Peripheral edema, early satiety, and epigastric or right upper quadrant fullness or discomfort may develop as the right heart fails (cor pulmonale). Some patients with CTEPH present after a small acute pulmonary embolus that may produce acute symptoms of right heart failure. A careful history brings out symptoms of dyspnea on minimal exertion, easy fatigability, diminishing activities, and episodes of angina-like pain or light-headedness. Further examination may reveal signs of pulmonary hypertension.

As is the case with symptoms, the physical signs of CTEPH are far from uniform. The physical examination may be surprisingly unrewarding if right heart failure has not occurred, even if the patient complains of severe dyspnea. Another challenge in diagnosis is that the physical signs of pulmonary hypertension are the same no matter what the underlying pathophysiology.

In the early stages, the jugular venous pulse is characterized by a large A wave. As the right heart fails, the V wave becomes predominant. The right ventricle is usually palpable near the lower left sternal border, and pulmonary valve closure may be audible in the second intercostal space. Occasional patients with advanced disease are hypoxic and slightly cyanotic. Cyanosis, if it is present at all, is usually peripheral and related to low cardiac output. Central cyanosis may be present from a persistent foramen ovale or atrial septal defect with right-to-left shunting. Clubbing is an uncommon finding.

Examination of the chest may be initially normal. Later, jugular venous distension with prominent A and V waves, as described above, may become evident. Auscultation of the chest may reveal some specific and nonspecific anomalies. The second heart sound is often narrowly split and varies normally with respiration; P2 is accentuated. A sharp systolic ejection click may be heard over the pulmonary artery. As the right heart fails, a right atrial gallop usually is present, and tricuspid insufficiency develops. Because of the large pressure gradient across the tricuspid valve in patients with pulmonary hypertension, the murmur is high pitched and may not exhibit respiratory variation. These findings are quite different from those usually observed in patients with tricuspid valvular disease. A murmur of pulmonic regurgitation may also be detected.

One specific sign is a flow murmur, which is heard especially over the back, beneath the scapula. Moser and colleagues[15] pointed out that murmurs are often heard in patients with CTEPH. The murmur is portrayed as maximal over the lung fields, increasing in intensity with inspiration, and frequently spilling beyond the second sound.[15] These murmurs probably result from turbulent flow past a segmental tapering, or it is also conceivable that they correspond to aggressive bronchial flow. An important observation is that these flow murmurs have not been described in patients with primary pulmonary hypertension, the major differential diagnosis for this condition.

Signs of chronic venous stasis may be present in the legs, with skin discoloration, and perhaps with healed varicosities or varicose ulcers. Peripheral edema is variable among patients and, if present, may be especially difficult to detect if the patient has chronic lower extremity venous stasis with or without ulceration.

Thus, the clinical signs and symptoms of CTEPH are not by any means specific and far from uniform. Suspicion for the diagnosis should be raised once the degree of symptomatology is out of proportion to the patient's general condition. Once the suspicion is made, the clinician should then pursue key points in the patient's past history and physical findings that may relate to this condition. The diagnosis, however, is only and finally confirmed with the aid of a broad variety of diagnostic modalities. Table 45-1 summarizes some of the patient characteristics at the authors' center encompassing the last 12 years, from 1998 to 2010, amongst over 1500 patients.

## DIAGNOSTIC MODALITIES

To ensure the diagnosis in patients with CTEPH, a consistent evaluation is recommended for all patients who present with unexplained pulmonary hypertension. The non-specificity of the clinical presentation and symptoms contribute to the

**TABLE 45-1: Preoperative Patient Characteristics in Over 1500 Patients**

| Variable | 1500 Patients (1998–2010) |
|---|---|
| Age (year) | 51.6 ± 15.4 |
| Pulmonary artery pressure (mm Hg) | |
| Systolic | 75.6 ± 18.9 |
| Diastolic | 28.0 ± 9.6 |
| Mean | 45.9 ± 11.5 |
| Pulmonary vascular resistance (dyne/s/cm$^5$) | 814.2 ± 431.5 |
| Cardiac output (L/min) | 4.1 ± 1.4 |
| Tricuspid regurgitant jet (M/s) | 4.2 ± 0.7 |
| In hospital >24 h preoperatively | 344 (22.9) |
| In ICU preoperatively | 27 (1.8) |
| On intravenous inotropes preoperatively | 42 (2.8) |
| Mechanical ventilation preoperatively | 7 (0.5) |
| NYHA class | |
| I | 22 (1.5) |
| II | 145 (9.7) |
| III | 1204 (80.3) |
| IV | 129 (8.6) |

Data are shown as mean ± standard deviation or numbers (percentages).
ICU, intensive care unit; NYHA, New York Heart Association.

diagnostic delay that most patients with CTEPH experience. In the authors' center it is common to see patients who have gone undiagnosed for several years, typically for 2 to 3 years.

The workup generally starts with a chest radiograph. Chest radiography may be deceptively normal in the early stages of CTEPH. However, with the development of significant pulmonary hypertension and right heart enlargement, some characteristic findings may tip the examiner toward the diagnosis. Central pulmonary arteries may be enlarged, and the right ventricle may also be enlarged without enlargement of the left atrium or ventricle, unlike mitral stenosis (Fig. 45-1). The chest radiograph may also show either apparent vessel cutoffs of the lobar or segmental pulmonary arteries, or regions of oligemia that suggest vascular occlusion. However, one should keep in mind that despite these classic findings, a large number of patients might present with a relatively normal chest radiograph, even in the setting of severe degrees of pulmonary hypertension. The electrocardiogram demonstrates findings of right ventricular hypertrophy (right axis deviation, dominant R wave in $V_1$).

Pulmonary function tests are necessary to exclude obstructive or restrictive intrinsic pulmonary parenchymal disease as the cause of the hypertension, but generally are not helpful. They reveal minimal changes in lung volume and ventilation; patients by and large have normal or slightly restricted pulmonary mechanics. Diffusing capacity of the lung for carbon monoxide (DLCO) often is reduced and may be the only abnormality on pulmonary function testing.

Most of these patients are hypoxic; room air arterial oxygen tension ranges between 50 and 83 torr, the average being 65 torr.[16] $CO_2$ tension is slightly reduced and is compensated by reduced bicarbonate. Dead space ventilation is increased. Ventilation–perfusion studies show a moderate mismatch with some heterogeneity among various respirator units within the lung and correlate poorly with the degree of pulmonary obstruction.[17]

The ventilation–perfusion lung scan is the essential test for establishing the diagnosis of unresolved pulmonary thromboembolism. An entirely normal lung scan excludes

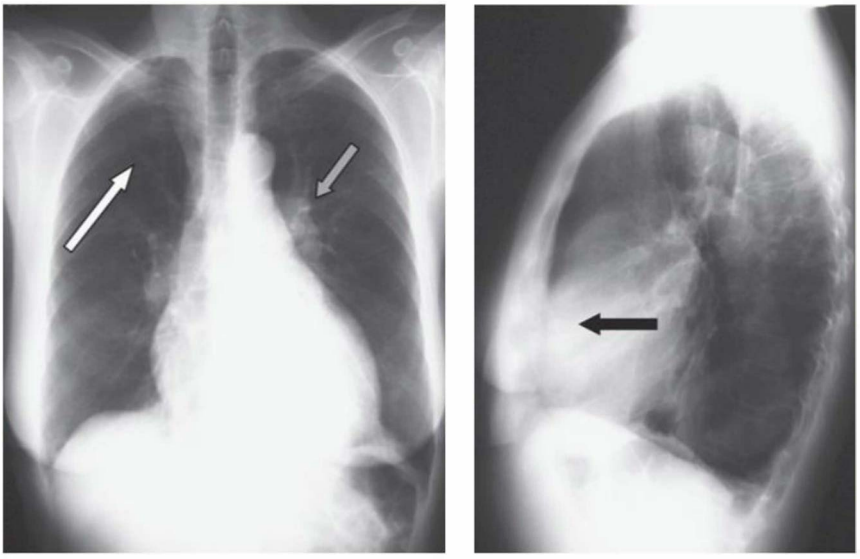


**FIGURE 45-1** Typical chest radiograph of a patient with chronic thromboembolic pulmonary hypertension. Note an enlarged right atrium and right ventricle (*black arrow on the lateral view*), disparity of size between the left and the right pulmonary arteries, and hypoperfusion in several areas of the lung (*white arrows*).

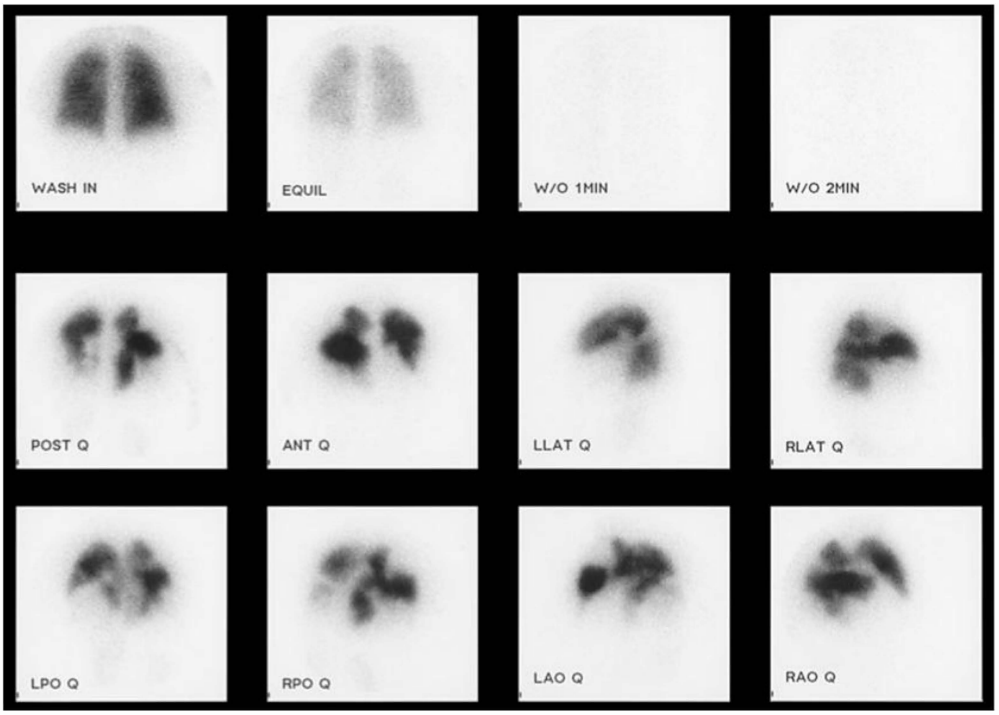



**FIGURE 45-2** Lung ventilation and perfusion study (V/Q scan) in a patient with chronic thromboembolic pulmonary hypertension. Note that the ventilation portion of the study is normal.

the diagnosis of both acute or chronic, unresolved thromboembolism. Patients with CTEPH invariably demonstrate one or more segmental or larger perfusion defects in lung regions that typically have normal ventilation (Fig. 45-2). The usual lung scan pattern in most patients with pulmonary hypertension either is relatively normal or shows diffuse non-uniform perfusion.[18–20] The magnitude of perfusion defects in chronic thromboembolic disease often underestimates the actual degree of vascular obstruction. When subsegmental or larger perfusion defects are noted on the scan, even when they are matched with ventilatory defects, pulmonary angiography is appropriate to confirm or rule out thromboembolic disease.

Right-heart catheterization and pulmonary angiography should be pursued in any patient with suspected chronic thromboembolic disease. Despite advances in computed tomography (CT) and the increasing reliance upon this imaging modality in the evaluation of the pulmonary vascular bed, its role in this population remains somewhat undefined, and pulmonary angiography should still be considered the gold standard in establishing the diagnosis of CTEPH. Organized thromboembolic lesions do not have the appearance of the intravascular filling defects seen with acute pulmonary emboli, and experience is essential for the proper interpretation of pulmonary angiograms in patients with unresolved, chronic embolic disease. Organized thrombi appear as unusual filling defects, webs, or bands, or completely thrombosed vessels that may resemble congenital absence of the vessel (Fig. 45-3).[20] Organized material along a vascular wall of a recanalized vessel produces a scalloped or serrated luminal edge. Because of both vessel-wall thickening and dilatation of proximal vessels, the contrast-filled lumen may appear relatively normal in diameter. Distal vessels demonstrate the rapid tapering and pruning characteristic of pulmonary hypertension (Fig. 45-3).

Historically, angiography in those with pulmonary hypertension has been thought to carry disproportionate risk. The authors have found this not to be the case and, at the authors' institution, pulmonary angiographies are performed daily in these patients with minimal associated risks. Several thousand angiograms in pulmonary hypertensive patients have now been performed at the authors' institution without mortality. Although some risk remains, the benefit of establishing the presence of a treatable cause of the hypertension far outweighs the small risk; pulmonary angiography should be performed whenever there is a possibility that chronic thromboembolism is the etiology of pulmonary hypertension.

In addition to pulmonary angiography, patients over 45 undergo coronary arteriography and other cardiac investigation as necessary. If significant disease is found, additional cardiac surgery is performed at the time of PEA.

In recent years, higher resolution helical CT scans of the chest have been used more frequently in diagnosing pulmonary thromboembolic disease. The presence of large clots in

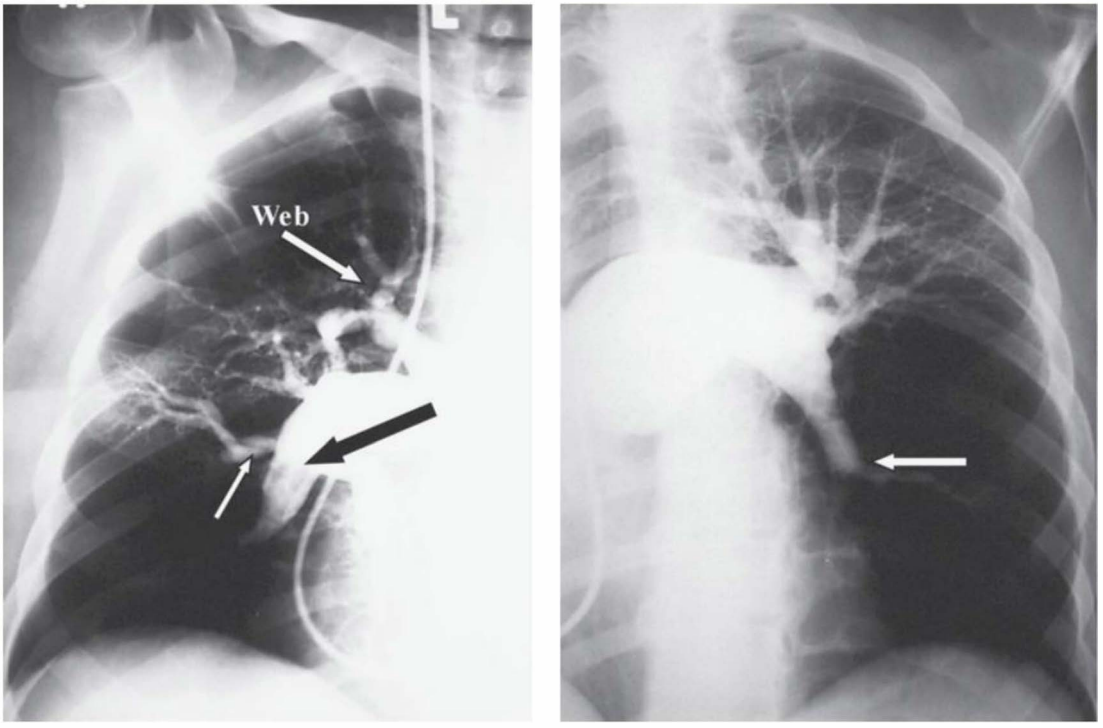



**FIGURE 45-3** Pulmonary angiogram in a patient with chronic thromboembolic pulmonary hypertension. Note the extensive areas of hypoperfusion as a result of complete occlusion, as well as luminal irregularities, webs, bands, and pouches, as shown by arrows.

lobar or segmental vessels generally confirms the diagnosis. CT features of CTEPH include evidence of organized thrombus lining the pulmonary vessels in an eccentric fashion, enlargement of the right ventricle and the central arteries, variation in size of segmental arteries, and parenchymal changes characteristic of pulmonary infarction. In addition, in rare situations in which there are concerns about external compression, or occlusion of main pulmonary arteries is present, CT scans can be helpful in differentiating thromboembolic disease from other causes such as mediastinal fibrosis, lymphadenopathy, or tumors. Although CT scans are considered the gold standard in the diagnosis of acute PE, pulmonary angiography is still the preferred method of diagnosis in chronic pulmonary thromboembolic disease. A patient should never be turned down for surgical treatment without a full evaluation, which includes pulmonary angiography.

## MEDICAL THERAPY

Medical therapy for CTEPH is of limited value and remains palliative at best. In light of the occlusive nature of this disease, there is no curative medical regimen that would alleviate the degree of pulmonary hypertension present in these patients. Right ventricular failure is generally treated with diuretics and vasodilators. Over the past decade, a wide variety of new medical therapies have been developed for the treatment of pulmonary hypertension. These include prostacyclin analogs, phosphodiesterase inhibitors, and endothelium receptor antagonists.[21–23] There has been an increased use of these medical therapies in patients with CTEPH. As a consequence, the authors have been seeing a significant delay in patient referrals, even in patients who have obviously operable disease. In 2010, 45 percent of patients with operable CTEPH referred for and who subsequently underwent surgery at the authors' center were taking one or more pulmonary vasodilator agents. Jensen et al.[24] reported an increased use of these medications from 19.9 percent in 2005 to 37 percent in 2007, in the absence of significant clinical or hemodynamic benefit, while suggesting that this approach resulted in delayed referral for surgery. Further studies are necessary and are currently ongoing to evaluate the efficacy and appropriate role for such therapies. Ultimately, it may be shown that there could be a role for these therapies in patients who have undergone PEA and still have residual pulmonary hypertension. However, these agents are practically useless in the setting of CTEPH, due to the fixed mechanical obstructive nature of the disease. Rarely, patients with CTEPH may experience temporary relief with medical management; this is not curative and symptoms do recur. These patients typically have secondary arteriopathy at the precapillary level and could potentially benefit from medical treatment once the mechanical obstruction has been

removed. In general, medical therapy should be regarded as only supportive, and should not delay referral for surgery. Similarly, the prognosis is unaffected by medical therapy.

Chronic anticoagulation represents the mainstay of the medical regimen. Anticoagulation is primarily used to prevent future embolic episodes, but it also serves to limit the development of thrombus in regions of low flow within the pulmonary vasculature. Inferior vena caval filters are also used routinely to prevent recurrent embolization. If caval filtration and anticoagulation fail to prevent recurrent emboli, immediate thrombolysis may be beneficial, but lytic agents are incapable of altering the chronic component of the disease.

## SURGICAL THERAPY

Surgical removal of the chronic thromboembolic material remains the only curative option for patients with CTEPH. In an experienced center, the procedure can be performed with low operative morbidity and mortality, and can produce tremendous hemodynamic benefit with excellent prognoses. The only other surgical alternative for these patients is transplantation. However, as mentioned earlier, the authors consider transplantation inappropriate for treatment of this disease and believe it to be obsolete in the management of patients with CTEPH. In light of the mortality and morbidity rates of patients on transplant waiting lists, the higher risk of the operation, and the less desirable or inferior survival rate (approximately 80 percent at 1 year at experienced centers for transplantation vs 95 percent for PEA), PEA is clearly the superior choice. Furthermore, PEA appears to be permanently curative, and the issues of a continuing risk of rejection and immunosuppression are not present.

Allison performed the first successful pulmonary "thromboendarterectomy" through a sternotomy, using surface hypothermia in 1960, but only fresh clots were removed.[25] This operation took place 12 days after a thigh injury that led to PE, and an endarterectomy was not performed. Since then, there have been reports of the surgical treatment of chronic pulmonary thromboembolism, but most of the surgical experience in PEA has been reported from the UCSD Medical Center. Braunwald commenced the UCSD experience with this operation in 1970, which now totals almost 2600 cases. The operation described below, using deep hypothermia and circulatory arrest, is now our standard procedure.

### Guiding Principles of the Operation

Once the diagnosis of thromboembolic pulmonary hypertension has been established firmly, the decision for operation is made based on the severity of symptoms and the general condition of the patient. In general, suitable candidates with CTEPH enjoy excellent hemodynamic results, with outstanding long-term prognoses. Early in the PEA experience, Moser and colleagues pointed out that there were three major reasons for considering endarterectomy: hemodynamic, alveolo-respiratory, and prophylactic.

The hemodynamic goal is to prevent or ameliorate right ventricular compromise caused by pulmonary hypertension. The respiratory objective is to improve respiratory function with the removal of a large ventilated but unperfused physiologic dead space. The prophylactic goal is to prevent progressive right ventricular dysfunction or retrograde extension of the obstruction, which might result in further cardiorespiratory deterioration or death. The authors' experience has added another prophylactic goal: the prevention of secondary arteriopathic changes in the remaining patent vessels.

Although the essential techniques of PEA are quite similar to other open-heart operations, several guiding principles are specific for this procedure. For pulmonary hypertension to be a major factor, both pulmonary arteries must be involved substantially. The surgery is therefore always bilateral, although the volume of chronic thromboembolic material may vary significantly between the two lungs. The only reasonable approach to both pulmonary arteries is through a median sternotomy incision. Historically, there were many reports of a unilateral operation, and occasionally this is still performed in inexperienced centers through a thoracotomy. However, the unilateral approach ignores the disease on the contralateral side, subjects the patient to hemodynamic jeopardy during the clamping of the pulmonary artery, and does not allow for good visibility because of the continued presence of bronchial blood flow. In addition, collateral channels develop in chronic thrombotic hypertension not only through the bronchial arteries but also from diaphragmatic, intercostal, and pleural vessels. The dissection of the lung in the pleural space via a thoracotomy incision therefore can be extremely bloody. The median sternotomy incision, apart from providing bilateral access, avoids entry into the pleural cavities and permits the ready institution of cardiopulmonary bypass.

A thorough and successful endarterectomy of the pulmonary arteries can only be performed in a bloodless field and under circulatory arrest. Cardiopulmonary bypass is therefore essential not only to ensure cardiovascular stability when the operation is performed, but also to allow cooling of the patient for periods of circulatory arrest. Exceptional visibility of the pulmonary vasculature is required, and a bloodless field is an absolute requirement to define an adequate endarterectomy plane and to then follow the PEA specimen deep into the subsegmental vessels. Because of the copious bronchial blood flow usually present in these cases, periods of circulatory arrest are necessary to ensure perfect visibility. Again, there have been sporadic reports of the performance of this operation without circulatory arrest. However, it should be emphasized that although endarterectomy is possible without circulatory arrest, a complete and full endarterectomy is not. Without a complete endarterectomy all the way to the distal tail ends of each branch, successful hemodynamic improvement is not achievable, leaving the patients with residual pulmonary hypertension and a subsequent poor prognosis in the short- and long terms.

The authors always initiate the procedure without circulatory arrest; depending on the collateral flow, a variable amount

of dissection is possible before the circulation is stopped, but never complete dissection. The circulatory arrest periods are limited to 20 min, with restoration of flow after each arrest. With experience, the endarterectomy is generally performed with a single period of circulatory arrest on each side.

A true endarterectomy in the plane of the media must be accomplished. It is essential to appreciate that the removal of visible thrombus is largely incidental to this operation. Indeed, in most patients, no free thrombus is present, and on initial direct examination, the pulmonary vascular bed may appear normal to an inexperienced eye. The early literature on this procedure is filled with reports of thrombectomy performed without a complete endarterectomy, and in these cases the pulmonary artery pressures did not improve, often with the resultant death of the patient.

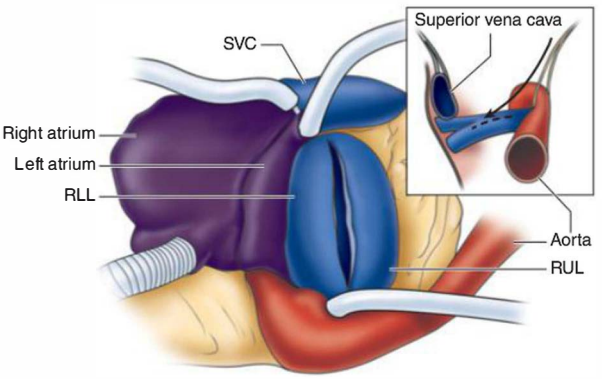



**FIGURE 45-4** Exposure of the right pulmonary artery. The incision is placed between the superior vena cava (SVC) and the aorta (as shown in the insert). It is imperative that the incision toward the right lower lobe artery is made in the middle of the vessel.

## Surgical Techniques

After a median sternotomy is performed, the pericardium is incised longitudinally and attached to the wound edges. Typically the right heart is enlarged, with a tense right atrium and a variable degree of tricuspid regurgitation. There is usually severe right ventricular hypertrophy. These patients are generally quite sensitive to any manipulation of the heart; with critical degrees of obstruction, the patient's condition may become quite unstable.

Anticoagulation is achieved with the use of beef-lung heparin sodium (400 units/kg, intravenously) administered to prolong the activated clotting time beyond 400 s. Full cardiopulmonary bypass is instituted with high ascending aortic cannulation and bicaval cannulation. The cannulae must be inserted into the superior and inferior vena cavae sufficiently to enable subsequent opening of the right atrium. The heart is emptied on bypass, and a vent is placed in the midline of the main pulmonary artery 1 cm distal to the pulmonary valve. This point can also be used to mark the beginning of the left pulmonary arteriotomy.

When cardiopulmonary bypass is initiated, surface cooling with both a head jacket and cooling blanket is begun. Cooling generally takes 45 min to 1 h. When ventricular fibrillation occurs, an additional vent is placed in the left atrium through the right superior pulmonary vein. This prevents atrial and ventricular distension from the large amount of bronchial arterial blood flow that is common in these patients.

The primary surgeon starts the operation on the patient's left side. During the cooling period, some preliminary dissection can be performed, with full mobilization of the right pulmonary artery from the ascending aorta. The superior vena cava is also fully mobilized. The approach to the right pulmonary artery is made medial, not lateral, to the superior vena cava. All dissection of the pulmonary arteries takes place intrapericardially, and neither pleural cavity should be entered. An incision is then made in the right pulmonary artery from beneath the ascending aorta out under the superior vena cava and entering the lower lobe branch of the pulmonary artery just after the take-off of the middle lobe artery (Fig. 45-4). It is important that the incision stays in the center of the vessel and continues into the lower, rather than the middle lobe artery.

A modified cerebellar retractor is placed between the aorta and superior vena cava. Upon opening the pulmonary artery a varying degree of loose thrombus may be present. This material is then removed to ensure good visualization of the vascular bed. It is most important to recognize that (1) an embolectomy without subsequent endarterectomy is quite ineffective, regardless of the amount of thromboembolic material, and (2) in most patients with chronic thromboembolic hypertension, direct examination of the pulmonary vascular bed at operation generally reveals no obvious embolic material. Therefore, to the inexperienced or cursory glance, the pulmonary vascular bed may well appear normal even in patients with severe chronic embolic pulmonary hypertension.

When the patient's temperature reaches 20°C, the aorta is cross-clamped and a single dose of cold cardioplegic solution (1 L) is administered. Additional myocardial protection is obtained with the use of a cooling jacket. The entire procedure is now performed with a single aortic cross-clamp period with no further administration of cardioplegic solution.

If the bronchial circulation is not excessive, the endarterectomy plane can be found during this early dissection. However, although a small amount of dissection can be performed before the initiation of circulatory arrest, it is unwise to proceed unless perfect visibility is obtained because the development of a correct plane is essential. Recognizing the plane is perhaps the most crucial and technically challenging part of the operation.

When blood obscures direct vision of the pulmonary vascular bed, thiopental is administered (500 mg to 1 g) until the electroencephalogram (EEG) becomes isoelectric. In most cases, the EEG is already isoelectric once the core temperature reaches 20°C. Circulatory arrest is then initiated, and the patient is exsanguinated. All monitoring lines to the patient are turned off to prevent the aspiration of air. Snares

are tightened around the cannulae in the superior and inferior vena cavae.

A microtome knife is used to develop the endarterectomy plane posteriorly, because any inadvertent egress in this site could be repaired readily, or simply left alone. Dissection in the correct plane is critical because if the plane is too deep, the pulmonary artery may perforate, with fatal results. If the dissection plane is not deep enough, inadequate amounts of the chronic thromboembolic material will be removed, leaving the patient with residual pulmonary hypertension.

Once the plane is correctly developed, a full-thickness layer is left in the region of the incision to ease subsequent repair. The endarterectomy is then performed with an eversion technique. Because the vessel is everted and subsegmental branches are being worked on, a perforation here will become inaccessible later. This is why the absolute visualization in a completely bloodless field provided by circulatory arrest is essential. It is important that each subsegmental branch is followed and freed individually until it ends in a "tail," beyond which there is no further obstruction. Residual material never should be cut free; the entire specimen should "tail off" and come free spontaneously. Although retrograde cerebral perfusion has been advocated for total circulatory arrest in other procedures, it is not helpful in this operation because it does not provide for a completely bloodless field. Furthermore, with the short arrest times that can be achieved with experience, it is not necessary.

Once the right-sided endarterectomy is completed, circulation is restarted, and the arteriotomy is repaired with a continuous 6-0 polypropylene suture. The hemostatic nature of this closure is aided by the nature of the initial dissection, with the full thickness of the pulmonary artery being preserved immediately adjacent to the incision.

After completion of the repair of the right arteriotomy, the surgeon moves to the patient's right side. The pulmonary vent catheter is withdrawn, and an arteriotomy is made in the left pulmonary artery lateral to the pericardial reflection, avoiding entry into the left pleural space. Additional lateral dissection does not enhance intraluminal visibility, may endanger the left phrenic nerve, and makes subsequent repair of the left pulmonary artery more difficult (Fig. 45-5). The left-sided dissection is virtually analogous in all respects to that accomplished on the right. The duration of circulatory arrest intervals during the performance of the left-sided dissection is subject to the same restriction as for the right.

After completion of the endarterectomy, cardiopulmonary bypass is reinstituted and warming is commenced. The rewarming period generally takes approximately 90 min but varies according to the body mass of the patient.

The pulmonary artery is then closed and the pulmonary arterial vent is replaced. The right atrium is then opened and examined. Any interatrial communication is closed. Although tricuspid valve regurgitation is invariable in these patients and is often severe, tricuspid valve repair is not performed. Right ventricular remodeling occurs within a few days, with the return of tricuspid competence. If other cardiac procedures are required, such as coronary artery bypass or mitral or aortic valve surgery, these are performed conveniently during the systemic rewarming period. Myocardial cooling is discontinued once all cardiac procedures have been concluded. The left atrial vent is removed, and the vent site is repaired. All air is removed from the heart and the aortic cross-clamp is removed.

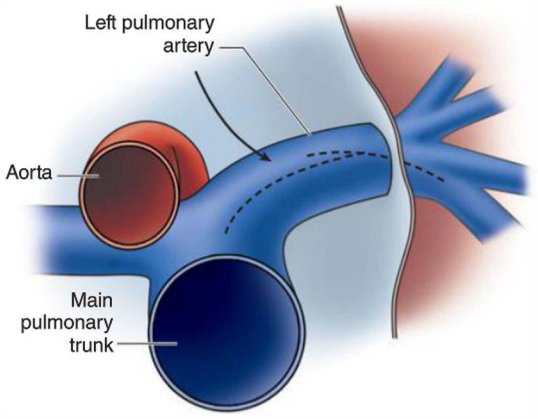



**FIGURE 45-5** Exposure of the left pulmonary artery with its corresponding incision. Note that the incision begins in the mid portion of the main pulmonary artery at the site of the insertion of the pulmonary artery vent.

When the patient has rewarmed, cardiopulmonary bypass is discontinued. Dopamine hydrochloride is routinely administered at renal doses, and other inotropic agents and vasodilators are titrated as necessary to sustain acceptable hemodynamics. The cardiac output is generally high, with a low systemic vascular resistance. Temporary atrial and ventricular epicardial pacing wires are placed.

Despite the duration of extracorporeal circulation, hemostasis is readily achieved, and the administration of platelets or coagulation factors is generally unnecessary. Wound closure is routine. A vigorous diuresis is usual for the next few hours, often a result of the previous systemic hypothermia.

## OUTCOMES/PROGNOSIS

The ages of the patients in our series have ranged from 8 to 86 years. A typical patient will have a severely elevated PVR level at rest, the absence of significant comorbid disease unrelated to right heart failure, and the appearances of chronic thrombi on angiogram that appear to be in balance with the measured degree of PVR. Exceptions to this general rule, of course, occur.

Although most patients have a PVR level in the range of 800 dyne/s/cm$^5$ and pulmonary artery pressures less than systemic, the hypertrophy of the right ventricle that occurs over time makes suprasystemic pulmonary hypertension possible. Therefore, many patients (perhaps 20 percent in the authors' practice) possess PVRs well in excess of 1000 dyne/s/cm$^5$ and suprasystemic pulmonary artery pressures. There is no

**TABLE 45-2: Preoperative/Postoperative Hemodynamic Results and Operating Times in 1500 Patients Since 1998**

| Variable | 1500 Patients (1998–2010) |
|---|---|
| PVR (dyne/s/cm$^5$) | 814.2 ± 431.5 |
| | 281.0 ± 188.5 |
| CO (L/min) | 4.1 ± 1.4 |
| | 5.5 ± 1.5 |
| Systolic PA pressure (mm Hg) | 75.6 ± 18.9 |
| | 45.1 ± 16.5 |
| Mean PA pressure (mm Hg) | 45.9 ± 11.5 |
| | 27.8 ± 9.7 |
| Tricuspid regurgitant velocity (M/s) | 4.2 ± 0.7 |
| | 3.0 ± 0.6 |
| **Operating times** | |
| Total operating room time (min) | 504.0 ± 78.3 |
| Surgical time (min) | 402.5 ± 71.7 |
| CPB time (min) | 243.0 ± 46.0 |
| Cross-clamp time (min) | 99.1 ± 26.5 |
| Circulatory arrest time (min) | 35.6 ± 12.5 |

Data are shown as mean ± standard deviation or number (percentages). Top numbers are preoperative values and bottom numbers are postoperative values. PVR, pulmonary vascular resistance; CO, cardiac output; PA, pulmonary artery; CPB, cardiopulmonary bypass.

upper limit of PVR, pulmonary artery pressure, or degree of right ventricular dysfunction that excludes patients from the operation. Table 45-2 compares the pre- and postoperative hemodynamic results as well as operating times at the authors' center.

As mentioned above, surgeons have become increasingly aware of the changes that can occur in the remaining patent (unaffected by clot) pulmonary vascular bed subjected to the higher pressures and flow that result from obstruction in other areas. Therefore, with the increasing experience and safety of the operation, the authors tend to offer surgery to symptomatic patients whenever the angiogram demonstrates thromboembolic disease. A rare patient might have a PVR that is normal at rest, but elevated with minimal exercise. This is usually a young patient with total unilateral pulmonary artery occlusion and unacceptable exertional dyspnea because of an elevation in dead space ventilation. Surgery, in this circumstance, is performed to reperfuse lung tissue, reestablish more normal ventilation–perfusion relationships (thereby reducing minute ventilatory requirements during rest and exercise), and preserve the integrity of the contralateral pulmonic circulation.

## Thromboembolic Classification and Surgical Outcome

There are four broad types of pulmonary vascular occlusive disease related to thrombus that can be appreciated. These




**FIGURE 45-6** Surgical specimen removed from right and left pulmonary arteries. Fresh thrombus in major arteries indicates of type I disease. Note that removal of only the fresh material leaves a large amount of disease behind. The ruler measures 15 cm.

types are based on the anatomical location of the thromboembolic material as well as vessel wall pathology. This classification allows one to estimate the patient's outcome and prognosis after an endarterectomy.[20,26,27] Type I disease (approximately 11 percent of cases of thromboembolic pulmonary hypertension; Fig. 45-6) refers to the situation in which major vessel clot is present and readily visible on the opening of the pulmonary arteries. As mentioned earlier, all central thrombotic material must be completely removed before the endarterectomy.

In type II disease (approximately 47 percent of cases; Fig. 45-7), no major vessel thrombus can be appreciated. In these cases, only thickened intima can be seen, occasionally

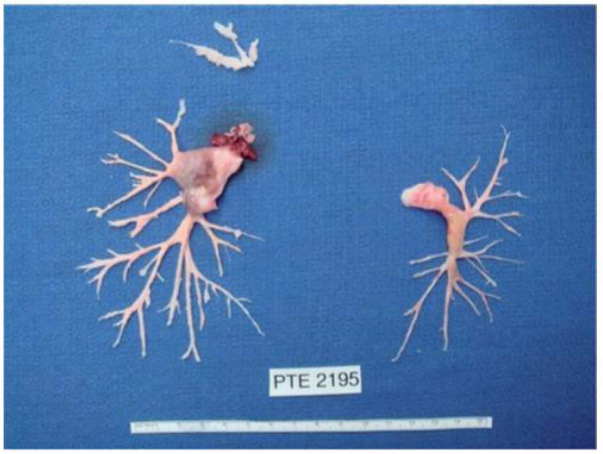



**FIGURE 45-7** Surgical specimen removed from right and left pulmonary arteries indicating evidence of type II disease. Note the extent of dissection down to the tail end of each one of the branches. The ruler measures 15 cm.

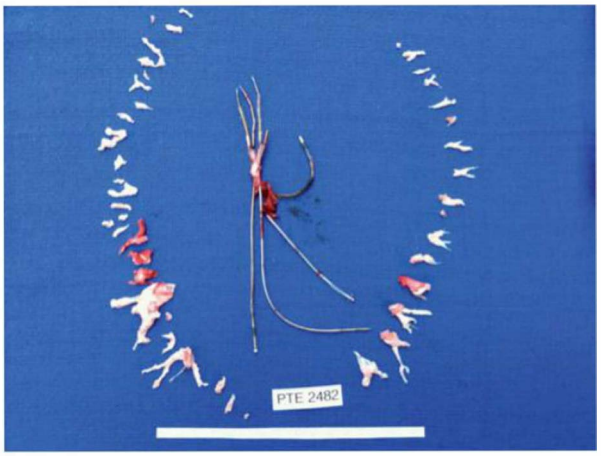



**FIGURE 45-8** Surgical specimen removed from right and left pulmonary arteries in a patient with type III disease secondary to pacemaker leads (*leads also removed as shown*). Note that in this patient the dissection plane has to be developed and raised at each segmental level. The ruler measures 15 cm.

**TABLE 45-3: Jamieson Surgical Thromboembolic Classification**

| Variable | 1500 Patients (1998–2010) |
|---|---|
| Jamieson disease classification (Different types on each side)[a] | |
| No thromboembolic disease or tumor | 33 (2.2) |
| Type I | 160 (10.7) |
| Type II | 710 (47.3) |
| Type III | 472 (31.5) |
| Type IV | 125 (8.3) |
| Jamieson disease classification (Same types on both sides)[b] | |
| Type I | 147 (9.8) |
| Type II | 427 (28.5) |
| Type III | 238 (15.9) |
| Type IV | 31 (2.1) |

Data are shown as number (percentages).

[a]The disease type was different on each side, the patient was categorized with the highest type.

[b]The disease type was similar in both lungs.

with webs, and the endarterectomy plane is raised in the main, lobar, or segmental vessels. Type III disease (approximately 32 percent of cases; Fig. 45-8) presents the most challenging surgical situation. The disease is very distal and confined to the segmental and subsegmental branches. No occlusion of vessels can be seen initially. The endarterectomy plane must be carefully and painstakingly raised in each segmental and subsegmental branch. Type III disease can be associated with presumed repetitive thrombi from indwelling catheters (e.g., pacemaker leads) or ventriculoatrial shunts.

Type IV disease (approximately 8 percent of cases; Fig. 45-9) does not represent primary thromboembolic pulmonary hypertension and is inoperable. It represents microscopic distal arteriolar vasculopathy without visible thromboembolic disease. In this entity, there is intrinsic small vessel disease, although secondary thrombus may occur as a result of stasis. Small-vessel disease may be unrelated to thromboembolic events ("primary" pulmonary hypertension) or occur in relation to thromboembolic hypertension as a result of a high-flow or high-pressure state in previously unaffected vessels similar to the generation of Eisenmenger syndrome. We believe that there may also be sympathetic "cross talk" from an affected contralateral side or stenotic areas in the same lung.

In general, patients with type IV disease will have residual pulmonary hypertension postoperatively, with no change in the levels of postoperative pulmonary vascular resistance (PVR), and unresolved postoperative tricuspid regurgitation. These patients generally require longer inotropic support, ventilatory support, and have longer ICU and hospital stays. They also have higher incidences of postoperative complications and, in fact, comprise the vast majority of the authors' perioperative morbidity and mortality. Table 45-3 indicates the breakdown of patients at the authors' center based on the type of the disease encountered in each lung.




**FIGURE 45-9** Surgical specimen removed from a patient with type IV disease. Note that despite the impressive appearance of the endarterectomy specimen, there are no distal tails. This patient had primary pulmonary hypertension and no change in pulmonary hemodynamics.

## Complications of Pulmonary Thromboendarterectomy

Patients with CTEPH are subject to all of the complications associated with open heart and major lung surgery (mediastinal bleeding, arrhythmias, pneumonia, atelectasis, wound infection, etc.). Table 45-4 summarizes the overall morbidity and mortality of PEA at the authors' center in the last 1500 patients. Furthermore, for comparison purposes, the table also shows the same complications in the last 500 patients. The most notable difference is the decline in mortality, which is now at 2.2 percent. In addition to the complications seen in

**TABLE 45-4: Perioperative Morbidity and Mortality in 1500 Patients Since 1998—Comparison is Made to the Last 500 Patients Since 2006**

| Complication | 1500 Patients (1998–2010) | 500 Patients (2006–2010) |
|---|---|---|
| Reperfusion edema | 202 (13.5) | 51 (10.2) |
| Pneumonia | 141 (9.4) | 49 (9.8) |
| Reoperative bleeding | 56 (3.7) | 19 (3.8) |
| Atrial fibrillation | 50 (3.3) | 22 (4.4) |
| Sepsis | 18 (1.2) | 5 (1.0) |
| Sternal wound infection | 18 (1.2) | 1 (0.2) |
| Hemothorax/pleural effusion | 17 (1.1) | 9 (1.8) |
| Dialysis | 15 (1.0) | 6 (1.2) |
| Pneumothorax | 11 (0.7) | 2 (0.4) |
| Pericardial effusion | 9 (0.6) | 4 (0.8) |
| GI bleeding | 8 (0.5) | 2 (0.4) |
| Sternal dehiscence | 8 (0.5) | 2 (0.4) |
| Chylothorax | 7 (0.5) | 2 (0.4) |
| Cerebrovascular accident | 3 (0.2) | 1 (0.2) |
| Deep venous thrombosis | 3 (0.2) | 1 (0.2) |
| Mortality | 62 (4.1) | 11 (2.2) |

Data are shown as number (percentages).

other forms of open heart and major lung surgery, patients who undergo PEA may develop complications specific to this operation. One such complication is the development of "reperfusion injury." This is a specific complication that is related to localized pulmonary edema. Reperfusion injury is defined as a radiologic opacity seen in the lungs within 72 h of PEA. This loose definition therefore may encompass many causes, such as fluid overload and infection.

True reperfusion injury that has a direct adverse impact on the clinical course of the patient occurs in approximately 13 percent of patients. In its most dramatic form, it occurs soon after operation (within a few hours) and is associated with profound desaturation. Edema-like fluid, sometimes with a bloody tinge, is suctioned from the endotracheal tube. Frank blood from the endotracheal tube, however, signifies a mechanical violation of the blood–airway barrier that has occurred at operation and stems from a technical error. This complication should be managed, if possible, by identification of the affected area by bronchoscopy and balloon occlusion of the affected lobe until coagulation can be normalized.

A common cause of reperfusion pulmonary edema (RPE) is persistent high pulmonary artery pressures postoperatively when a thorough endarterectomy has been performed in certain areas, but a large part of the pulmonary vascular bed is still affected by type IV changes. However, the reperfusion phenomenon is also occasionally encountered in patients after a seemingly technically perfect operation with complete resolution of high pulmonary artery pressures. In these cases, the response may be one of reactive hyperemia after the revascularization of segments of the pulmonary arterial bed that have long experienced no flow. Other contributing factors may include perioperative pulmonary ischemia and conditions associated with high-permeability lung injury in the area of the now denuded endothelium. Fortunately, the incidence of this complication has declined in the authors' series, probably as a result of the more complete and expeditious removal of the endarterectomy specimen that has come with the large experience over the last two decades.

## Management of the Reperfusion Pulmonary Edema

Early measures should be taken to minimize the development of RPE with diuresis, maintenance of the hematocrit, and the early use of peak end-expiratory pressure. Once the capillary leak has been established, treatment is supportive because RPE eventually will resolve if satisfactory hemodynamics and oxygenation can be maintained. Careful management of ventilation and fluid balance is required. The hematocrit is kept high (31–35 percent), and the patient should undergo aggressive diuresis, even if this requires ultrafiltration. The patient's ventilatory status may be dramatically position s ensitive. The $Fio_2$ level is kept as low as is compatible with an oxygen saturation of 90 percent. A careful titration of positive end-expiratory pressure is carried out, with a progressive transition from volume- to pressure-limited inverse ratio ventilation and the acceptance of moderate hypercapnia. The use of steroids is discouraged because they are generally ineffective and may lead to infection. Infrequently, inhaled nitric oxide at 20 to 40 parts/million can improve gas exchange. On rare occasions, the authors have used extracorporeal perfusion support (extracorporeal membrane oxygenator or extracorporeal carbon dioxide removal) until ventilation can be resumed satisfactorily, usually after 7 to 10 days.

## Results of Pulmonary Thromboendarterectomy

PEA is now performed at several major cardiovascular centers around the world; the greatest experience with this operation has been at UCSD Medical Center, where the technique was pioneered and has been refined to its current state over the past two decades. Nearly 2600 pulmonary endarterectomies have now been performed.

The mean age for the authors' patients is 51.6 years, with a range of 8 to 86, and no significant gender difference. In nearly a third of the patients, at least one additional cardiac procedure is generally performed at the time of operation. Most commonly, the concurrent procedure is closure of a patent foramen ovale or atrial septal defect (26 percent) or coronary artery bypass grafting (8 percent).

An immediate reduction of pulmonary pressures and vascular resistance down to normal levels is generally achieved. These hemodynamic accomplishments are usually permanent. The right heart failure rapidly resolves as does the tricuspid regurgitation. These changes are usually evident immediately postoperatively, or as late as a few days later on

follow-up transthoracic echocardiograms. Patients experience a dramatic improvement in their symptoms, and have a very low risk of recurrence so long as they are anticoagulated and have received a preoperative inferior vena caval filter.

An analysis of the authors' data encompassing a time span of 30 years indicates an operative mortality of about 8 percent. However, in a study published in 2003 by the authors,[26] an overall mortality of 4.4 percent was reported. In the authors' most recent series since 2006 including over 500 patients, the mortality has now dropped to 2.2 percent. Furthermore, when considering isolated PEA, without any additional procedures and excluding patients with sarcomas, there has been zero mortality over the past 2 years and in over 260 patients at the author's center. This reflects the learning curve for performing this operation safely and the refinements in surgical technique that have occurred.

With growing experience, the authors are now able to offer this procedure to some very high-risk patients with an overall mortality rate of about 2.2 percent. The majority of patients enjoy dramatic hemodynamic improvement postoperatively. A reduction in pulmonary arterial pressures and resistances to normal levels and a corresponding improvement in pulmonary blood flow and cardiac output are generally immediate and sustained. Echocardiographic studies have demonstrated that, with the elimination of chronic pressure overload, right ventricular geometry rapidly reverts toward normal. Right atrial and right ventricular enlargement regresses. Tricuspid valve function returns to normal within a few days as a result of restoration of tricuspid annular geometry after the remodeling of the right ventricle, and therefore tricuspid repair is not part of the operation. In general, these changes can be assumed to be permanent. Before the operation, more than 95 percent of the patients are in New York Heart Association (NYHA) functional class III or IV; at 1 year after the operation, 95 percent of patients remain in NYHA functional class I or II.[20,28,29]

## SUMMARY

It is increasingly apparent that pulmonary hypertension caused by chronic PE is a relatively common condition, which is under recognized and carries a poor prognosis. Medical therapy is ineffective in prolonging life in these patients and improves symptoms only transiently. The only therapeutic alternative to PEA is lung transplantation. The advantages of endarterectomy over transplantation include a lower operative morbidity and mortality and excellent long-term results without the risks associated with chronic immunosuppression and chronic allograft rejection. The mortality for endarterectomy at the authors' institution is now in the range of 2.2 percent, with sustained benefit. These results are clearly superior to those for transplantation in both the short- and long-term.

Although PEA is technically demanding for the surgeon, requiring careful dissection of the pulmonary artery planes and the use of circulatory arrest, excellent short- and long-term results can be achieved. PEA can now be offered to patients with an acceptable mortality rate and excellent anticipation of clinical improvement. With this growing experience, it has also become clear that unilateral PEA is obsolete and that circulatory arrest is an essential measure.

Despite an increase in awareness over the past two decades, and a continuous effort in education through publications and presentations, the principal difficulty in treating CTEPH is the lack of recognizing the condition. Increased understanding of both the prevalence of this condition and the possibility of a surgical cure should give more patients an opportunity for relief from this debilitating and ultimately fatal disease.

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## SURGICAL TREATMENT OF CHRONIC PULMONARY THROMBOEMBOLIC DISEASE BOARD REVIEW QUESTIONS (CHAPTER 45)

1. What percentage of patients with acute PE will go on to develop CTEPH?
   A. 15 to 20 percent
   B. 10 to 15 percent
   C. 5 to 10 percent
   D. 3 to 5 percent
   E. Less than 2 percent

2. Once the mean pulmonary artery pressure exceeds 50 mm Hg, the 3-year mortality is approximately:
   A. 10 percent
   B. 20 percent
   C. 40 percent
   D. 75 percent
   E. 90 percent

3. Which of the following is the gold standard for diagnosing CTEPH?
   A. Pulmonary function testing
   B. Ventilation–perfusion scan
   C. Pulmonary angiography
   D. Transesophageal echocardiography
   E. CT angiography

4. A 48-year-old male is diagnosed with severe pulmonary hypertension secondary to chronic thromboembolic disease. The pulmonary pressures are suprasystemic and the PVR exceeds 1000 dyne/s/cm$^2$. The V/Q scan is severely abnormal with multiple large bilateral perfusion defects. The pulmonary angiogram shows complete occlusion of the bilateral lower lobes as well as webs in the upper lobe branches. Which of the following is the best course of action?
   A. Continue anticoagulation and diuretic therapy
   B. Continue anticoagulation and diuretic therapy; add medical therapy for pulmonary hypertension
   C. Continue anticoagulation and diuretic therapy; add medical therapy for pulmonary hypertension; reassess pressures in 6 months
   D. Proceed with surgical therapy
   E. Decline further therapy due to irreversible pulmonary hypertension

5. Which of the following is the correct technique for PEA?
   A. Median sternotomy, cardiopulmonary bypass, moderate hypothermia with low flow during pulmonary endarterectomy
   B. Thoracotomy with femoral bypass if necessary and periods of low flow during endarterectomy
   C. Median sternotomy, cardiopulmonary bypass, and periods of deep hypothermic circulatory arrest during endarterectomy
   D. Thoracotomy with femoral cardiopulmonary bypass and periods of deep hypothermic circulatory arrest during endarterectomy of the distal vessels
   E. Median sternotomy, cardiopulmonary bypass, inflow occlusion of pulmonary arteries to allow bloodless field during endarterectomy

## ANSWERS

1. **Answer: D.** It is estimated that about 3 to 5 percent of patients that survive an acute PE will develop pulmonary hypertension as the result of chronic thromboembolic disease.
2. **Answer: E.** Prognosis for pulmonary hypertension is quite poor and 3-year mortality reaches 90 percent once the mean pulmonary artery pressure reaches 50 mm Hg.
3. **Answer: C.** Pulmonary angiography is the definitive test for the proper diagnosis of CTEPH, as it defines anatomic features and establishes the degree of pulmonary hypertension.
4. **Answer: D.** The patient has chronic thromboembolic pulmonary hypertension and further medical intervention is unlikely to be effective. Surgical intervention is indicated.
5. **Answer: C.** In order to access both lungs and perform a complete distal endarterectomy into the segmental and subsegmental branches, median sternotomy with full cardiopulmonary bypass is required. Periods of deep hypothermic circulatory arrest provide the necessary bloodless field during the endarterectomy.

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# Role of Surgery in Management of Hypertrophic Cardiomyopathy

*Hartzell V. Schaff*

**KEY CONCEPTS**

- Hypertrophic cardiomyopathy (HCM) can be defined as left ventricular hypertrophy in the absence of an underlying cause (e.g., hypertension, aortic stenosis). Left ventricular outflow tract obstruction (LVOTO) results from septal hypertrophy combined with systolic anterior motion of the mitral valve, which also produces variable degrees of mitral regurgitation.
- The distribution of left ventricular hypertrophy is variable in patients with HCM. The appearance and severity of the hypertrophy do not correlate with genotype; multiple ventricular morphologies may be found in the same family. The most common pattern of hypertrophy is diffuse involvement of the ventricular septum.
- Myocardial fiber disarray is a characteristic feature of HCM.
- Although coronary arteries are larger than normal in patients with HCM and basal coronary flow is increased at rest, coronary flow reserve is decreased in symptomatic HCM patients.
- Two-dimensional and Doppler echocardiography is essential in the diagnosis of HCM. Cardiac MRI is useful in identifying regions of left ventricular hypertrophy not easily seen with echocardiography, specifically the anterolateral free wall and apex, and the presence and severity of myocardial fibrosis.
- Symptoms in HCM patients are often associated with the development of LVOTO.
- Transaortic septal myectomy is indicated in HOCM patients who continue to have limiting symptoms despite medical treatment (i.e., β-blockade, calcium antagonists, disopyramide). Mitral valve replacement is reserved for patients with intrinsic leaflet abnormalities that cannot be repaired.
- Adequate septal myectomy usually yields 3 to 12 g of muscle. Intraoperative simultaneous aortic and left ventricular pressure measurements can be used to confirm complete relief of LVOTO after septal myectomy. The most common cause of inadequate myectomy is failure to extend the myectomy far enough toward the cardiac apex.
- Unroofing of coronary artery muscle bridges is performed selectively, particularly in young patients and those experiencing anginal symptoms.
- Mortality risk with septal myectomy is less than 1 percent in experienced centers with over 90 percent of patients experiencing improvement of at least two functional classes. Late recurrence of large resting left ventricular outflow tract gradients is very uncommon after successful myectomy.
- Alcohol septal ablation is an alternative to myectomy in high-risk HCM patients. It has been associated with an 11-percent incidence of complete heart block requiring permanent pacemaker and a 1.5-percent hospital mortality.

## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) may be defined as left ventricular (LV) hypertrophy in the absence of an underlying cause such as systemic hypertension or valvular aortic stenosis.[1] Left ventricular outflow tract obstruction (LVOTO) is caused by septal hypertrophy combined with abnormal systolic anterior motion (SAM) of the mitral valve, and this, in turn, produces variable degrees of mitral valve regurgitation (MR). LVOTO in HCM is distinct in morphology and

prognosis from congenital membranous subaortic stenosis, which is rarely associated with SAM. Some patients with HCM will have symptoms due to mid ventricular obstruction. Hypertrophic obstructive cardiomyopathy (HOCM) is important for surgeons because obstruction may occur in over 70 percent of patients with HCM,[2] and transaortic septal myectomy is highly effective in the management of HOCM.

## Morphology

### DISTRIBUTION OF HYPERTROPHY

As shown in Figure 46-1 distribution of LV hypertrophy is variable in patients with HCM. For example, subaortic stenosis may be associated with diffuse ventricular hypertrophy (Fig. 46-1E), or the hypertrophy may be limited to the septum (asymmetric septal hypertrophy, ASH) (Fig. 46-1B). In other patients, there may be obstruction in the mid-ventricle where hypertrophy of the papillary muscles leads to obstruction of ejection of blood, and in other patients, there may be an apical distribution of hypertrophy (Fig. 46-1F). It is important to note that neither the phenotype of the disease nor the appearance and severity of hypertrophy correlates with genotype; multiple ventricular morphologies may be found in the same family.

### MITRAL VALVE

In the classic form of HOCM, the mitral valve, especially the anterior leaflet of the valve, moves anteriorly during systole, and the posterior leaflet closes against the mid- and free-edge third of the anterior leaflet instead of at the free edge as occurs normally. The free edge of the anterior

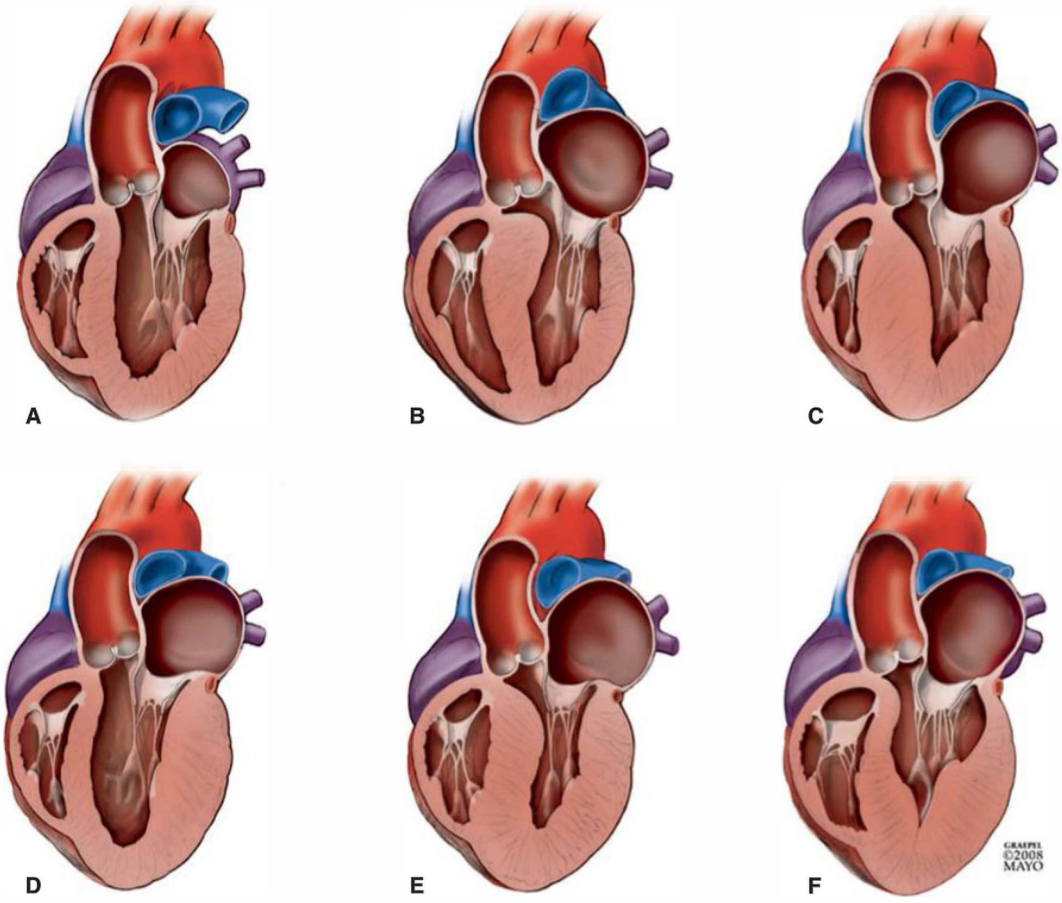



**FIGURE 46-1** Morphologic subtypes of hypertrophic cardiomyopathy. Hypertrophy may be localized t o the basal septum as in panel **B**, diffuse as in panel **E**, or predominantly apical as shown in panel **F**. Normal ventricular morphology is shown in panel **A**. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

leaflet is then displaced upward and narrows the left ventricular outflow tract (LVOT). Anterior displacement of the valve leaflets produces MR of variable degree, and the jet is oriented in a posterolateral direction. MR is an important pathophysiologic component of HOCM and contributes to the symptoms of dyspnea and fatigability. Apposition of the anterior leaflet to the bulging septum produces a contact lesion, a whitish endocardial scar, which is useful in guiding septal myectomy. It is important to note that occurrence of SAM is often dynamic, and provocative maneuvers such as Valsalva, squatting, exercise, and, in some cases, adrenergic stimulation may be necessary to elicit SAM, MR, and LVOTO.

Anomalies of papillary muscles are present in 15 to 20 percent of patients with HCM who undergo myectomy. These abnormalities include anomalous papillary muscles, direct insertion of papillary muscles into the anterior mitral valve leaflet, fusion of the papillary muscle to the ventricular septum or LV free wall, and accessory muscles and accessory anomalous chordae (false cords). In most cases, these abnormalities do not complicate myectomy or contribute to outflow tract obstruction, but in some patients, anomalous papillary muscles, especially those that insert directly into the anterior leaflet, can contribute to outflow tract obstruction.[3]

### CORONARY ARTERIES

Coronary arteries are larger than normal in patients with HCM, and basal coronary flow is increased in the resting state. Coronary flow reserve (CFR), however, is decreased in symptomatic patients with HCM compared with controls, and phasic flow is abnormal with a greater amount of flow during diastole, the presence of flow reversal in systole, and a more rapid deceleration of diastolic blood flow compared with normal patients. Decreased flow reserve is associated with a reduction in coronary resistance, suggesting that the mechanism is not due to narrowing of intramyocardial small arteries or compression of the microcirculation; indeed, the reduction in CFR in patients with HCM may be the result of near maximal vasodilation of the microcirculation in the basal state.

Atherosclerotic coronary artery disease (CAD) is present in approximately 5 to 15 percent of patients with HCM depending upon the population studied. At the Mayo Clinic, significant CAD was detected in half of patients who were selected for coronary angiography, and disease was severe in 26 percent.[4] Survival of HCM patients with obstructive CAD is reduced compared with HCM patients without CAD, and survival is also poorer than in patients without HCM who have comparable CAD and normal ventricular function.

Muscular bridging of the left anterior descending coronary artery (LAD) is not uncommon, occurring in 15 percent of patients with HCM undergoing coronary angiography at our clinic. It is unclear whether bridging of the LAD plays a role in the pathophysiology of the disease and associated symptoms of angina, but for adult patients, risk of death and, in particular, sudden cardiac death, is not increased among patients with HCM with myocardial bridging. In contrast, Yetman and coworkers[5] reported that among children with HCM, systolic compression of the LAD was present in 285 cases and was associated with a greater incidence of chest pain (60 vs 19 percent, $P = 0.04$), cardiac arrest with subsequent resuscitation (50 vs 4 percent, $P = 0.004$), and ventricular tachycardia (80 vs 8 percent, $P < 0.001$). Myocardial ischemia was postulated to be the cause of this poor outcome.

## Histopathology

### MYOCARDIAL FIBER DISARRAY

A characteristic histologic feature of HCM is myocardial fiber disarray, which consists of short runs of severely hypertrophied fibers interspersed by connective tissue. Myocytes show large, bizarre nuclei with degenerating muscle fibers and fibrosis. It is the disorganized whirling of muscle fibers that is characteristic of HCM. Myocardial disarray is not pathognomonic for HCM and may be present in the myocardium for any conditions in which there is pressure overload.

# GENETICS

HCM has a prevalence of 0.2 percent for phenotypically expressed disease. Approximately 60 to 80 percent of cases are familial and the remainder result from de novo mutations.[6] HCM is genetically diverse, involving sarcomeric and nonsarcomeric proteins, and over 400 mutations in over 15 genes have been identified; indeed, double and compound heterozygosity and homozygosity have been reported.[7] Most patients with familial disease have mutations in three protein-encoding genes: β-myosin heavy chain (MYH7) in 35 to 50 percent, myosin-binding protein C (MYBPC3) in 15 to 25 percent, and cardiac troponin T type 2 (TNNT2) in 15 to 20 percent. In current practice, the clinical value of genetic testing is uncertain.

A potential benefit of genetic analysis is the preclinical diagnosis in patients with a family history of SCD or in those carrying a "malignant" mutation that predisposes them to a severe phenotype. Also, it may be useful to know the precise genetic defect in HCM among asymptomatic family members who carry the mutation and might be at risk for SCD.

# PATHOPHYSIOLOGY

## Diastolic Dysfunction

Diastolic dysfunction with elevation of the LV end-diastolic pressure is the principal pathophysiologic feature in HCM. The resulting increase in left atrial and pulmonary venous

pressures accounts for the common symptoms of effort dyspnea and limited aerobic capacity. With worsening diastolic function, LV filling becomes more dependent on atrial contraction, and occurrence of atrial arrhythmias, especially atrial fibrillation (AF), can cause an acute and profound decrease in cardiac output and worsening of symptoms.

LVOTO has a direct effect of increasing end-diastolic pressure and an indirect effect on hemodynamics through the often associated MR. Thus, while surgical myectomy has a minimal immediate effect on overall LV mass, symptoms related to diastolic dysfunction are immediately improved when outflow gradients and MR are relieved. A secondary effect of septal myectomy on diastolic function is regression of hypertrophy.

In some patients, concentric ventricular hypertrophy is so severe that muscle mass encroaches upon the ventricular cavity and reduces normal cavity size. This is particularly striking in patients with the apical form of HCM where the distal one-third to distal one-half of the left ventricle may be obliterated (during diastole and systole) by muscle. Surgical remodeling by apical myectomy may increase end-diastolic volume and thus improve diastolic function.

## Left Ventricular Outflow Obstruction

Surgical treatment of HCM consists primarily of relief of LVOTO. Previously, there was debate on the importance of outflow tract obstruction as a mechanism for symptoms in patients with HCM because of the lability of the finding and the question of catheter entrapment when gradients were measured by invasive catheterization. It is now recognized that outflow obstruction is much more common than previously thought, correlates importantly with development of symptoms, and may negatively influence long-term survival.

Among 320 patients with HCM, Maron found resting outflow tract gradients of ≥50 mm Hg in 37 percent and, more importantly, found exercise-induced gradients (mean 80 ± 43 mm Hg) in an additional 106 patients. Thus, as many as 70 percent of patients with HCM who come to clinical evaluation will have significant outflow tract obstruction.[8] Another important finding in this study was the relative unreliability of the Valsalva maneuver (sensitivity 40 percent) compared with exercise Doppler echocardiography in detecting these dynamic gradients. Latent obstruction can also be documented during hemodynamic catheterization by isoproterenol challenge, and the technique may be useful in patients who are unable to exercise or in patients in whom reliable Doppler echocardiographic parameters cannot be measured.[9]

## Mitral Valve Regurgitation

As is true with outflow gradients, the degree of MR is often dynamic. Symptomatic patients with moderate or severe degrees of MR associated with HOCM are excellent candidates for operation because the MR and associated symptoms (dyspnea and fatigability) are almost always abolished or significantly improved with adequate septal myectomy.

Intrinsic mitral valve disease may contribute to valvular regurgitation in patients with HOCM. Rupture of chordae with resultant leaflet prolapse can precipitate congestive heart failure, and hemodynamics may worsen if HCM is not recognized and patients are managed medically with afterload reduction.

## Echocardiogram

Two-dimensional and Doppler echocardiography is the essential tool for the diagnosis of HCM, providing information on ventricular morphology, hemodynamics, and valve function. The most common pattern of hypertrophy is diffuse involvement of the ventricular septum. In patients with HCM, the average maximal LV-wall thickness is 20 to 22 mm, and in 5 to 10 percent of patients, LV wall thickness is dramatically increased measuring 30 to 50 mm. Morphology of the septum appears to vary according to age, and older patients with HCM often demonstrate a sigmoid configuration.

The echocardiographic findings of increased wall thickness should prompt a search for other causes including systemic hypertension (especially in patients on dialysis), valvular aortic stenosis, and infiltrative and glycogen storage diseases such as cardiac amyloidosis, Fabry's disease, and Friedreich's ataxia.

On continuous-wave Doppler echocardiography, LVOTO is seen as a high-velocity, late-peaking, "dagger-shaped" signal. In patients with low velocity at rest (less than 3 m/s), maneuvers such as Valsalva, inhalation of amyl nitrate, or exercise may demonstrate latent obstruction. Presence and severity of MR can be determined by Doppler color-flow imaging. It is important to differentiate the true outflow tract velocity from the MR jet.

MR that results from SAM is eccentric and directed posterolaterally during late systole. A centrally directed jet should raise suspicion of a primary leaflet abnormality contributing to valve leakage. Preoperative transesophageal echocardiography (TEE) is unnecessary in most patients, but TEE is critically important intraoperatively in assessing the results of myectomy.

## Cardiac MRI

Cardiac MRI is useful in identifying regions of LV hypertrophy not easily recognized by echocardiography, specifically the anterolateral free wall and the apical area. In addition, MRI can detect the presence and severity of myocardial fibrosis that appears to be an important risk factor for subsequent ventricular arrhythmias and sudden cardiac death.

## Invasive Catheterization

In current practice, cardiac catheterization is rarely necessary for the diagnosis of HCM. Coronary angiography is indicated for patients with symptoms of angina and for patients at risk for CAD (strong family history, abnormal lipids, older age) who undergo myectomy. A hemodynamic study with isoproterenol provocation can be useful in identifying patients with labile obstruction gradients that cannot be elicited during echocardiography.

# NATURAL HISTORY

## Symptom Course

The clinical course of HCM is variable, but the onset of symptoms is often associated with development of LVOTO. It is uncertain what causes this in adult patients who have had no gradients until the fourth, fifth, or sixth decade of life. Onset of AF can also precipitate symptoms and predispose to systemic embolism, which occurs in 6 percent of patients.[10] AF is noted in 30 percent of older patients with HCM.

Infective endocarditis may occur with HCM, and the reported incidence is 1.4 cases/1000 person-years. But the important feature is that in virtually all cases of endocarditis, there is LVOTO. Indeed, among HCM patients with obstruction, the incidence of endocarditis is 3.8 per 1000 person-years, or a 4 percent likelihood of developing this complication over 10 years.

## Survival

In the general population, survival of patients with HCM is similar to individuals without disease, and early reports of high mortality in HCM may be explained by excess numbers of high-risk patients included in studies from tertiary referral centers. More recent data indicate that the annual mortality rate of patients with HCM is approximately 1 percent, but there are several important subgroups that have higher risk of cardiac death; indeed, HCM is the most common cause of sudden death among young athletes.

## Obstructed vs Nonobstructed HCM

Until recently, there was uncertainty and debate on the influence of LVOTO on survival of patients with HCM. Convincing studies by Maron et al.,[11] Autore and associates,[12] and Elliot and coworkers[13] have demonstrated a strong correlation between resting outflow gradients and late risk of death. In a longitudinal study of 1101 patients with HCM, Maron et al. reported that patients with outflow tract obstruction (a basal gradient of at least 30 mm Hg) had a risk of death from HCM or symptom progression that was more than four times that observed among patients

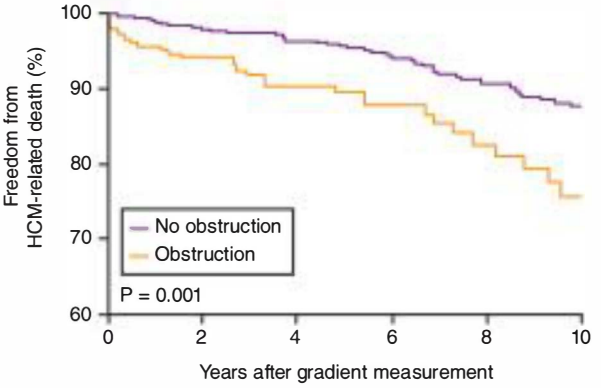



**FIGURE 46-2** Survival of patients with hypertrophic cardiomyopathy with and without obstruction (≥30 mm Hg). This analysis includes only deaths related to HCM. (Reproduced with permission from Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;348:295–303. Copyright Massachusetts Medical Society.)

without obstruction (Fig. 46-2). The association of outflow tract obstruction on limiting symptoms and death was independent of other clinical variables. Of note, patients with obstruction and mild symptoms (NYHA class II) were more likely to have progression to severe symptoms or die from heart failure than asymptomatic patients with cardiomyopathy (Fig. 46-3).

An important clinical question is whether the prognosis of asymptomatic HOCM patients with high gradients can be improved by septal reduction. Elliot et al. report that the risk of sudden death is relatively low (<0.4 percent per year) in asymptomatic patients with LVOTO and none

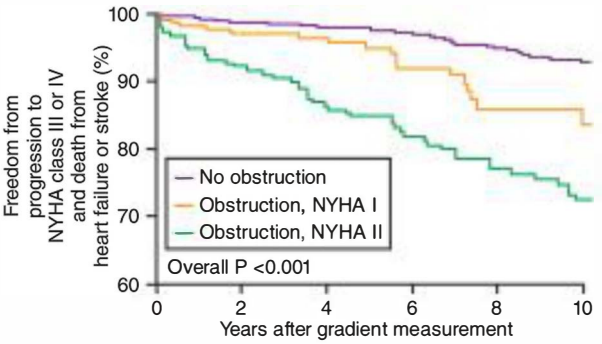



**FIGURE 46-3** Probability of progression to severe heart failure, death, or stroke in patients without obstruction and in patients with outflow tract obstruction stratified by presence or absence of symptoms. (Reproduced with permission from Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;348:295–303. Copyright Massachusetts Medical Society.)

of the recognized risk factors for SCD; but their study did demonstrate reduced survival among patients with LVOTO and nonsustained ventricular tachycardia, abnormal exercise blood pressure response, a family history of premature sudden death, unexplained syncope, or severe LV hypertrophy.[13]

The prognosis of patients with latent obstruction is less clear, but a study by Vaglio et al. suggests that the clinical course is similar to patients with resting obstruction.[14] In their series, one-quarter of patients required invasive therapy for relief of symptoms, and the annual mortality was 2 percent per year, a rate higher than that reported for patients with HCM and no LVOTO.

### Use of Implantable Cardioverter-Defibrillator

SCD is a special concern in HCM, and there is debate on the appropriate use of implantable cardioverter-defibrillators (ICDs) for primary and secondary prevention of SCD. Variables that appear to identify patients at increased risk of arrhythmic events include prior cardiac arrest or sustained ventricular tachycardia, a family history of premature sudden death due to HCM, repetitive nonsustained ventricular tachycardia on ambulatory Holter monitoring, massive ventricular hypertrophy (wall thickness greater than 30 mm), and hypotensive response to exercise. Other findings such as myocardial bridging in young patients or myocardial fibrosis detected by cardiac MRI may also increase the risk of sudden death.

Consensus among experts holds that an ICD is strongly warranted for secondary prevention of SCD in patients with prior cardiac arrest or sustained and spontaneously occurring ventricular tachycardia, and should be considered in patients with multiple clinical risk factors and in selected patients with a single major risk factor such as a history of SCD in a close relative. For patients who need an ICD implant and are referred for septal myectomy, we prefer to delay device implantation until the third or fourth day postoperatively and avoid the potential for lead dislocation if the ICD is placed immediately preoperatively.

## SURGICAL TREATMENT

### Indications for Operation

Septal myectomy is, in general, reserved for patients who continue to have limiting symptoms despite medical treatment. Pharmacological therapy usually begins with β-adrenergic blocking agents, which have a negative inotropic effect and may mitigate latent outflow gradients provoked with exercise. β-Blockers are less effective in reducing resting gradients. The calcium antagonist, Verapamil, has been used for patients with nonobstructive and obstructive HCM. The drug may improve ventricular relaxation and decreased LV contractility, but hemodynamic and electrophysiologic side effects limit long-term use. Disopyramide has negative inotropic effects and is a type I-A antiarrhythmic agent that can improve symptoms by reducing resting gradients. However, this drug also has side effects including dry mouth and eyes, constipation, and difficulty in micturition. Also, it increases atrioventricular nodal conduction and thus may increase ventricular rate in patients with AF. It is important to realize that although medications may ameliorate symptoms, drug therapy does not appear to decrease the probability of sudden death. In a recent study of 173 patients who were taking amiodarone, β-blockers, verapamil, and/or sotalol for treatment of symptoms, there was no difference in sudden death mortality compared with patients who were on no pharmacologic therapy.[15] Thus, ICDs remain the primary therapy used for prevention of sudden death in high-risk HOCM patients.

### Technique of Operation

Operation is performed through a median sternotomy, and normothermic cardiopulmonary bypass is established in the standard fashion using a single, two-staged venous cannula. The aorta is cross-clamped, and cold blood cardioplegia (1000–1200 mL) is infused through the aortic needle vent to arrest the heart. Adequate exposure of the subaortic septum is critically important, and several maneuvers facilitate the operation. First, pericardial sutures are used only on the right side to elevate the pericardium toward the surgeon. Next, an oblique aortotomy is made slightly closer to the sinotubular ridge than is usual for aortic valve replacement, and the incision is carried through the midpoint of the noncoronary aortic sinus of Valsalva to a level approximately 1 cm above the valve annulus. The edge of the proximal aorta is held out of the way with small stay sutures, and a cardiotomy sucker is placed through the aortic valve and used to depress the anterior leaflet of the mitral valve and protect it from injury. The right aortic valve cusp is collapsed against the sinus wall where it will usually stay. A sponge stick is used to depress the right ventricle and rotate the septum posteriorly, orienting the LV outflow anteriorly.

A standard No. 10 scalpel blade is used for myectomy; incision in the septum begins just to the right of the nadir of the right aortic sinus (Fig. 46-4). The incision in the septum is made upward and then leftward over to the anterior leaflet of the mitral valve. Scissors are used to complete excision of this initial portion of the myocardium. The area of septal excision is then deepened and lengthened toward the apex of the heart being certain to excise hypertrophied septum beyond the endocardial scar. Trabeculations are excised, and the myectomy site is further enlarged with the use of pituitary rongeurs. Adequate septal myectomy usually yields 3 to 12 g of muscle. Use of the sponge stick to depress the heart posteriorly will improve exposure of the distal extent of the myectomy. The aortotomy is closed and the operation proceeds as usual.

This technique for a more extended myectomy[16] differs from the standard Morrow operation in which parallel incisions create a trough in the septum that extends up to 3 cm from the aortic valve; wider excision of muscle in the immediate subaortic area improves exposure of the distal extent of

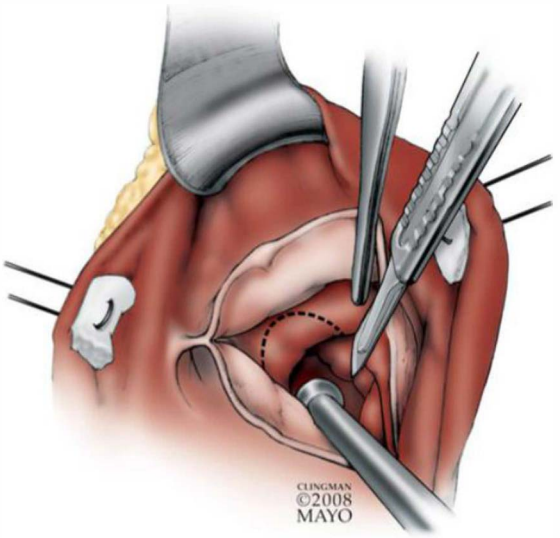



**FIGURE 46-4** Septal excision begins just to the right of the nadir of the right aortic sinus and extends leftward toward the anterior leaflet of the mitral valve. After the initial specimen is removed, the area of septal excision should be carried toward the apex of the heart well past the endocardial scar. A wider proximal area of excision improves exposure of the more distal extent of septectomy. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

the hypertrophied septum, and excision extends up to 7 cm from the aortic valve. Inadequate myectomy results more often from failure to excise sufficient length of the septum (toward the apex) than from inadequate depth of excision. Importantly, the methods described above have proved adequate for all patients with subaortic obstruction, and maneuvers such as anterior leaflet plication are unnecessary and potentially harmful. Mitral valve replacement is reserved for patients with intrinsic leaflet abnormalities that cannot be repaired. To confirm complete relief of the LVOTO, we routinely measure simultaneous aortic and LV pressure by direct needle puncture before and after myectomy. If the resting LVOT gradient is diminished by the effects of anesthesia, premature ventricular beats are induced by stimulating the ventricle to elicit the dynamic gradient produced by the Brockenborough phenomenon; the postextrasystolic contraction is more forceful due to increased contractility and decreased afterload. The same maneuver is then repeated after myectomy. Intraoperative TEE can identify residual MR, SAM, and any septal defects created by excision of septal muscle.

Unroofing of coronary artery bridging is performed in selected cases, particularly young patients and those who have angina preoperatively. After identification of the coronary artery distal to the intramyocardial segment, the anterior surface of the vessel is exposed by sharp dissection that is continued proximally until the LAD reemerges onto the epicardium. The divided myocardium over the artery is usually 3 to 5 mm thick. If the course of the artery is so deep that trabeculations of the right ventricular cavity are entered, pledgeted sutures placed deep to the coronary artery can repair the opening into the ventricle.

# OUTCOMES

## Early Results

### MORTALITY

Risk of hospital death after isolated septal myectomy for HOCM is low, generally less than 1 percent in experienced centers (Fig. 46-5). Surgical risk may be higher among very elderly patients (particularly those with severe disabling symptoms associated with pulmonary hypertension), patients with prior myectomy, or those requiring concomitant procedures.

### MORBIDITY

Complications such as complete heart block requiring permanent pacemaker and iatrogenic ventricular septal perforation have become uncommon (≤1–2 percent). Partial or complete left bundle branch block is a frequent finding after surgical myectomy but is not associated with adverse

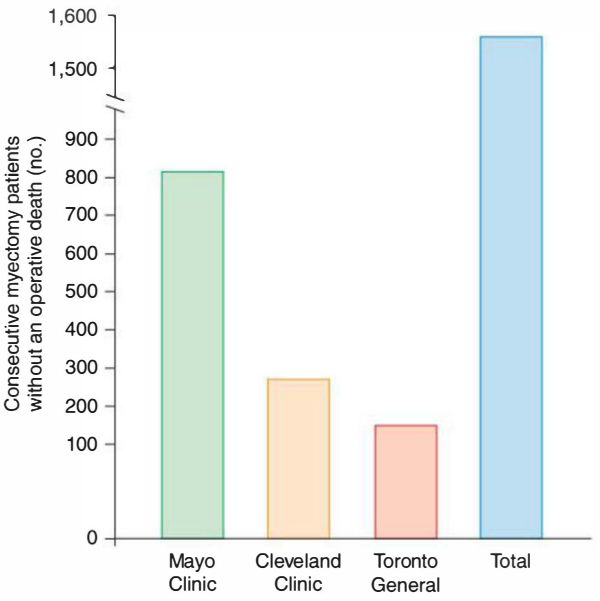



**FIGURE 46-5** Operative risk of isolated septal myectomy for hypertrophic cardiomyopathy is less than 1 percent and approaches zero in centers with broad experience with the procedure. (Reproduced with permission from Maron BJ. Surgical myectomy remains the primary treatment option for severely symptomatic patients with obstructive hypertrophic cardiomyopathy. *Circulation* 2007;116:196–206. Copyright Wolters Kluwer Health.)

sequelae. However, if the patient has complete right bundle branch block preoperatively, interruption of the left bundle after myectomy increases risk of complete heart block. This is particularly important in patients who have had alcohol septal ablation prior to operation. Elbardissi et al. reported that the risk of postoperative pacemaker insertion was 36 percent in patients who underwent alcohol septal ablation before myectomy compared with 3 percent for those without prior intervention.[17]

## Late Results

### SYMPTOM RELIEF

Improvement in symptoms and exercise capacity after myectomy is highly predictable and durable; over 90 percent of severely symptomatic patients have improvement of ≥ two function classes. Indeed, relief of outflow gradients by myectomy is equally effective in improving limitation due to dyspnea, angina, or syncope. Importantly, symptomatic benefit of myectomy is directly related to reducing the basal outflow gradient and MR and restoring normal LV systolic and end-diastolic pressures (in more than 90 percent of patients) which, in turn, may also favorably influence LV diastolic filling and myocardial ischemia. Relief of the gradient may decrease left atrial size and the subsequent risk of developing AF.

Late recurrence of large resting LV outflow gradients is very uncommon after successful myectomy in either adults or children with HOCM; this is in contrast to patients who have surgery for relief of congenital membranous subaortic stenosis. The most common causes of recurrent symptoms and obstruction are limited myectomy at the initial operation, mid-ventricular obstruction, and anomalies of papillary muscles. Most often, inadequate myectomy at initial operation is due to failure to extend the myectomy far enough toward the apex of the heart.[18]

## SURVIVAL

Septal myectomy is usually performed for relief of symptoms, but there is evidence that operation may improve survival of patients with HOCM. In the report of Ommen et al., late survival of 289 patients with HOCM undergoing septal myectomy was 98, 96, and 83 percent 1, 5, and 10 years postoperatively, and this survival was similar to that of an age- and sex-matched US population and similar to survival of HCM patients without obstruction (Fig. 46-6). In the same study, myectomy patients had superior survival free from all-cause mortality ($P < 0.001$), HCM-related mortality ($P < 0.001$), and SCD ($P = 0.003$) compared with unoperated HCM patients with obstruction (Fig. 46-7). On multivariable analysis, performance of myectomy had a strong, independent association with survival (hazard ratio 0.43; $P < 0.001$).

Recent studies also suggest mechanisms whereby relief of LVOT gradients might improve survival. The extent of

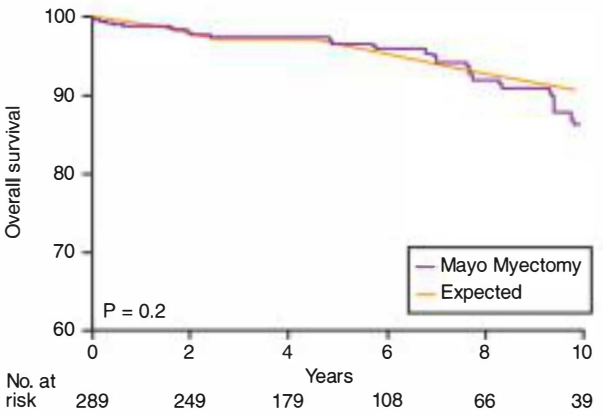



**FIGURE 46-6** Survival of patients with hypertrophic obstructive cardiomyopathy after septal myectomy is similar to and age and gender matched population. (Reproduced with permission from Ommen SR, Maron BJ, Olivotto I, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;46:470–476. Copyright Elsevier.)

LV hypertrophy is an important determinant of survival in patients with HCM, and successful myectomy results in some regression of LV hypertrophy.[19,20] Thus, patients with the obstructive form of HCM may have an additive burden of ventricular hypertrophy caused by pressure overload that is relieved by successful myectomy. Although the severity of LVH is a determinate of survival in unoperated patients, left ventricular mass and wall thickness are not predictors of late survival in HCM patients following myectomy.[21]

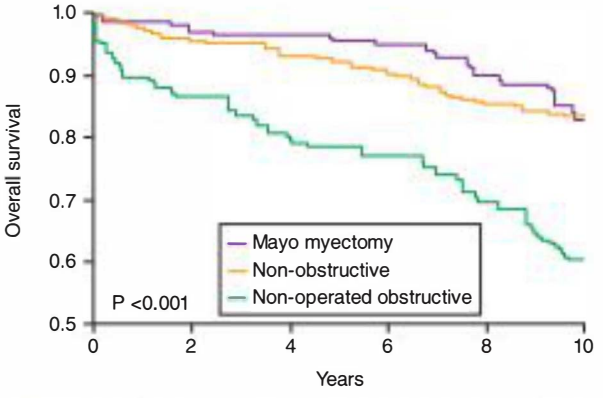



**FIGURE 46-7** Survival free from all-cause mortality in three hypertrophic cardiomyopathy patient subgroups: Mayo Clinic surgical myectomy ($n = 289$), non-operated with obstruction ($n = 228$), and non-obstructive ($n = 820$). Myectomy vs non-operated obstructive hypertrophic cardiomyopathy, $P < 0.001$; myectomy vs non-obstructive hypertrophic cardiomyopathy, $P = 0.8$. (Reproduced with permission from Ommen SR, Maron BJ, Olivotto I, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;46:470–476. Copyright Elsevier.)

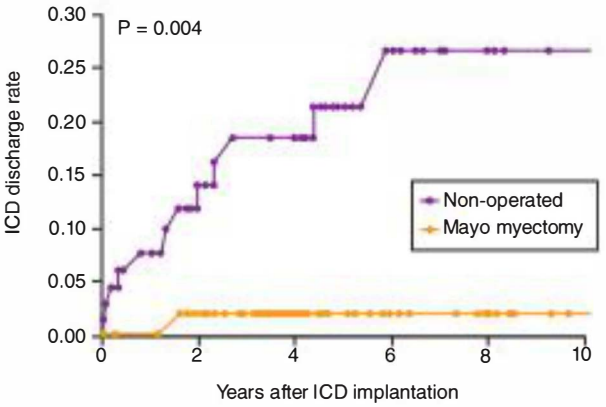



**FIGURE 46-8** Implantable cardioverter defibrillator discharge rates among patients with HCM who had septal myectomy compared with non-myectomy patients. Average annualized implantable cardioverter defibrillator discharge rates of 0.24 percent in the myectomy group, compared with 4.3 percent in the non-myectomy group ($P = 0.004$). (Reproduced with permission from McLeod CJ, Ommen SR, Ackerman MJ, et al. Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. *Eur Heart J* 2007;28:2583–2588. Copyright Oxford University Press.)

Additional insights on improved survival of myectomy patients come from McLeod and associates who reviewed patients with HCM who had received ICDs.[22] During follow-up (median 4.5 years), 12 patients (17 percent) in the non-myectomy group and only 1 patient (2 percent) in the myectomy group had appropriate ICD discharges (Fig. 46-8). The average annualized event rate was 4.3 percent/year in the non-myectomy group, compared with 0.24 percent/year following myectomy ($P = 0.004$). Thus, surgical myectomy and relief of outflow gradient are associated with a marked reduction in the incidence of appropriate ICD discharges and risk of SCD.

## COMPARISON TO SEPTAL ARTERY ABLATION

Septal reduction can be achieved by selective infarction of septal branches of the LAD, and the advantages of avoiding surgical incision and hospitalization are obvious. In a review of alcohol septal ablation from 42 published studies (2959 patients), resting LVOT gradient decreased from 65 to 16 mm Hg ($P < 0.001$), basal septal diameter reduced from 21 to 14 mm ($P < 0.001$), and hospital mortality was 1.5 percent.[23] However, the incidence of complete heart block requiring permanent pacemaker was 11 percent, and other important complications included coronary dissection (1.8 percent), pericardial effusion (0.6 percent), ventricular fibrillation (2.2 percent), stroke (1.1 percent), new right bundle branch block (46 percent), and new left bundle branch block (6.5 percent). Also, symptoms persisted in 11 percent of patients, redo alcohol ablation was required in 6.6 percent, and surgical myectomy was necessary in 2.0 percent. Thus, while this procedure is less invasive, it is not without significant morbidity and mortality.

Not all patients with HOCM are candidates for alcohol septal ablation because of unfavorable coronary anatomy. Also, concern has been raised about the potential long-term risk of sudden death related to arrhythmogenic substrate from the resulting septal scar. Cardiac magnetic resonance imaging demonstrates that, in most patients, alcohol septal ablation causes transmural tissue necrosis, located more inferiorly in the basal septum than myectomy; the infarct usually extends into the right ventricular side of the septum and sometimes spares the basal septum leading to residual gradients at follow-up. Thus, alcohol septal ablation is an option for patients who may have increased risk for operation, but septal myectomy remains the gold standard for patients with HCM and severe LV outflow obstruction who are refractory to maximal medical therapy.

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## ROLE OF SURGERY IN MANAGEMENT OF HYPERTROPHIC CARDIOMYOPATHY BOARD REVIEW QUESTIONS (CHAPTER 46)

1. Which of the following is *not* true regarding morphology of HCM?
   A. The phenotype closely correlates with the genotype.
   B. Up to 20 percent of patients will have anomalies of the papillary muscles.
   C. Coronary flow reserve is reduced.
   D. CAD is present in 5 to 15 percent of patients.
   E. LAD muscular bridging is found in 15 percent.

2. Which of the following histopathologic and genetic findings is true in patients with HCM?
   A. The myocardial fibers are hypertrophied and arranged in parallel sheets.
   B. There is organized whirling of the fibers.
   C. Most cases are not familial.
   D. It is a genetically diverse disease.
   E. All family members should undergo genetic testing.

3. HCM results in:
   A. Systolic dysfunction
   B. LVOTO
   C. Functional mitral stenosis
   D. Asymmetric left ventricular free wall thickening
   E. Central mitral insufficiency due to SAM

4. Surgical repair of HCM may include all of the following *except*:
   A. Septal myectomy
   B. Incision of the ventricular wall below the commissure between the left and right coronary cusps
   C. Mitral valve replacement
   D. Unroofing of the LAD
   E. Extension of the ventricular incision toward the apex

5. Results after surgery for HCM include?
   A. Operative mortality of 5 percent
   B. Heart block and pacemaker incidence of 5 percent
   C. Relief of symptoms in over 90 percent of patients
   D. Long-term survival below the general population
   E. Higher incidence of new bundle branch block compared with septal alcohol ablation

## ANSWERS

1. **Answer: A.** The phenotype of HCM is not closely associated with the genotype, and there is widely variable expression.
2. **Answer: D.** HCM is genetically diverse, even within close family members. The histopathology is characterized by disorganization of the muscle fibers.
3. **Answer: B.** The asymmetric septal wall thickening results in left ventricular outflow tract obstruction. There is associated diastolic dysfunction and asymmetric mitral insufficiency due to SAM.
4. **Answer: B.** The incision for the septal myectomy begins just below the nadir of the right coronary cusp, not at the commissure. Mitral valve replacement and unroofing of muscular bridging of the LAD may also be required.
5. **Answer: C.** The vast majority of patients have relief of symptoms after surgery and enjoy survival equivalent to the general population. Both operative mortality and pacemaker requirement are less than 5 percent. There is a higher incidence of new bundle branch block after alcohol ablation.

# 47

# Pericardial Disease

*Eric J. Okum*
*Abe DeAnda Jr.*

## KEY CONCEPTS

- Epidemiology
  - Pericarditis and pericardial effusions have many etiologies, including inflammation, infection, immunologic disorders, malignancy, myxedema, uremia, pregnancy, aortic dissection, cardiac rupture, trauma, myocardial infarction, cirrhosis, and heart failure. The three most common etiologies are neoplasia, uremia, and idiopathic causes. Cardiac tamponade usually is caused by bleeding, followed by other sources of chronic effusions.
- Pathophysiology
  - The pathophysiology of pericardial inflammation relates to the underlying causes of pericardial effusions and pericarditis. Effusions generally arise when pericardial fluid production exceeds reabsorption. With pericardial tamponade, there is a rapid increase in intrapericardial pressure and diminished diastolic compliance, ultimately resulting in equalization of right and left atrial, right and left ventricular, pulmonary artery wedge, and intrapericardial pressures. Pericarditis arises from inflammation of the pericardial sac. In constrictive pericarditis, there is a limitation in cardiac filling that is reflected in a "square root" sign seen in ventricular pressure tracings during cardiac catheterization.
- Clinical features
  - The symptoms of pericardial effusions include dyspnea, fever, and chest pain, although many effusions are asymptomatic. The signs include a pericardial friction rub, global electrocardiogram (ECG) changes, and pulsus paradoxus. Cardiac tamponade presents as hypotension and decreased cardiac output; Beck's triad includes muffled heart sounds, elevated venous pressure, and decreased systemic arterial pressure. Significant constrictive pericarditis manifests with symptoms of right-sided heart failure, including jugular venous distention, worsening peripheral edema, and pleural effusions.
- Diagnostics
  - Echocardiography is the gold standard for the diagnosis of pericardial effusions. Cardiac tamponade is a clinical diagnosis but can be confirmed or substantiated with echocardiography. Computed tomography is useful in identifying the thickened pericardial sac in patients with pericarditis, although magnetic resonance imaging is more sensitive and specific in diagnosing constrictive pericarditis. Right and left cardiac catheterization is the gold standard for diagnosing constrictive pericarditis.
- Treatment
  - Pericardial effusions are treated most readily with drainage, pericardiocentesis, or a pericardial window. Adjunctive medical therapy can be successful, depending on the etiology of the effusion. Depending on the etiology, tamponade can be treated with pericardiocentesis, a pericardial window, or surgical (re)exploration. Medical treatment of constrictive pericarditis is predicated on treating the underlying cause; however, the mainstay of therapy is pericardiectomy.
- Outcomes and prognosis
  - The outcomes and prognoses for pericardial effusions and tamponade depend on the etiology. Early mortality for pericardiectomy ranges from 5 to 10 percent, with 5-year survival ranging from 65 to 90 percent. Predictors of poor outcome are prior radiation, renal insufficiency, poor ventricular function, pulmonary hypertension, New York Heart Association functional class IV, hyponatremia, ascites, and hyperbilirubinemia.

# INTRODUCTION

## Historical Highlights

Galen was the first to describe pericardial disease in animals (circa 160 AD) and subsequently described in two patients the surgical drainage of purulent pericardial effusions.[1] This predated Lower's 1669 description of pericarditis in humans.[2] There are apocryphal references of penetrating heart wounds being treated, usually by the removal of the offending object, without much information about how subsequent drainage of the pericardial space was dealt with. Francisco Romero, a Catalonian physician, was probably the first heart surgeon, earning this title when he performed open drainage of a pericardial effusion in 1801. He presented this work 15 years later, but it was silenced for being too aggressive.[3] This predates the "birth of heart surgery" by almost 100 years, when Rehn first successfully sutured a heart wound in 1896.[4]

In 1929, Beck showed experimentally that constrictive pericarditis could be produced and treated surgically in laboratory animals[5,6] using Dakin's solution. His observations of the extent of the adhesions formed (and the concomitant neovascular supply) probably contributed to his later procedures for ischemic heart disease.[7] Pericardiectomy was then translated to clinical practice. By 1941, Blalock reported a series of 28 patients[8] who had undergone this procedure.

This chapter focuses on many aspects of pericardial disease including cardiac tamponade, pericardial effusion, and pericarditis, with an emphasis on the surgical aspects of this disease.

## Anatomy

The pericardium is a conical sac that encloses the heart and great vessels. It is located posterior to the body of the sternum, bounded by the second and sixth costal cartilages anteriorly and thoracic vertebrae 5 to 8 posteriorly. The ascending aorta, pulmonary artery, and the superior vena cava exit from the cephalad opening of the pericardium. The base is fused with the central tendon of the diaphragm. Loose connective tissue called the sternopericardial ligaments attaches the anterior surface of the pericardium to the posterior table of the sternum.

The pericardium is composed of an outer and inner membrane. A thick layer termed the fibrous pericardium is external, while a thin transparent membrane called the serous pericardium is internal. The serous pericardium is further divided into parietal and visceral layers. The former is fused to the fibrous portion, while the latter is reflected onto the epicardium. The visceral layer of the serous pericardium is in fact the epicardium of the heart, and thus is also in continuity with the adventitia of the coronary vessels. The thin layer of fluid between the two layers allows the heart to move in a near-frictionless environment.

By virtue of the anatomic reflection of the pericardium, two sinuses exist—the transverse and the oblique pericardial

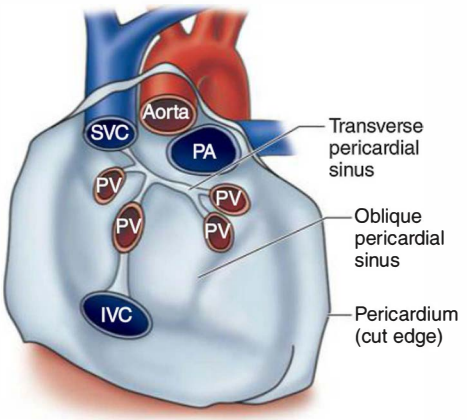



**FIGURE 47-1** Pericardial attachments and reflections. PA, pulmonary artery; PV, pulmonary vein; IVC, inferior vena cava; SVC, superior vena cava. (Reproduced with permission from Mangi AA, Torchiana DF. Pericardial disease. In: Cohn LH, Edmunds LH Jr (eds). *Cardiac Surgery in the Adult 2/3.* New York, NY: McGraw-Hill Publishers, 2003:1359–1372.)

sinuses (Fig. 47-1). The transverse sinus is located behind the ascending aorta and pulmonary trunk. If the pericardium is opened anteriorly, one can place a finger easily into this space and go from right lateral to left lateral pericardium. The larger sinus is the oblique sinus, which cradles the heart. One can see this space when the heart is lifted toward the right shoulder. This is a blind cul-de-sac, bordered to the right by the inferior vena cava (IVC). This therefore prevents passage around the IVC without sharp dissection. The two sinuses lie in near continuity with only a thin layer of serous pericardium separating the two.

The arterial supply of the pericardium comes mainly from the internal thoracic arteries. Smaller branches of the bronchial, esophageal, and superior phrenic arteries also contribute to the blood supply. The visceral layer of the serous pericardium is supplied by the coronary arteries. Venous drainage flows into the internal thoracic veins and azygous system. Nervous supply comes from the vagus, phrenic, and sympathetic trunks.[9]

## Embryology

The pericardium is derived, beginning the third week of gestation, from the progressive invagination of the intraembryonic coelomic cavity. This results in a creation of the visceral and parietal layers of the serous membrane, which will later become the serous pericardium. By the fourth week, with growth of the lung buds, pleuropericardial membranes are developed on each side. With continued growth and eventual fusion of the pleuropericardial membranes, the thoracic cavity becomes separated into the pericardial and two pleural cavities. This membrane will become the fibrous

pericardium. It is the failure of these membranes to fuse which results in congenital defects of the pericardium.[10]

## PERICARDIAL EFFUSION

### Epidemiology

The finding of a pericardial effusion is common in modern day cardiology and cardiothoracic surgical practices. The evolution and prevalence of noninvasive technology [i.e., echocardiography (ECHO)] has made the diagnosis of pericardial effusion both easier and apparently more frequent. Such incidental effusions are often discovered while patients are being evaluated for cardiac valvular disease. But many systemic processes other than cardiac can contribute to the development of pericardial effusions. All types of pericarditis (discussed later in this chapter) can lead to the development of effusions. Etiologies of pericarditis include infection, inflammation, immunologic disorders, malignancy, myxedema, uremia, pregnancy, aortic dissection, cardiac rupture, trauma, chylopericardium, postmyocardial infarction, cirrhosis, heart failure, and idiopathic.[11] Tuberculosis now is an uncommon cause of pericardial effusion but once was one of the more frequent etiologies of infective pericarditis. The clinical constellation of hemodynamic compromise, cardiomegaly, pleural effusion and large pericardial effusion were more common in those with tuberculosis than either malignancy or idiopathic causes.[12]

Multiple studies have shown the three most common etiologies for pericardial effusion to be neoplasia, uremia, and idiopathic.[13–15] Approximately 40 percent of these patients present with cardiac tamponade (discussed later).

### Pathophysiology

The pathophysiology of pericardial effusion relates to the underlying cause. As described above, fluid naturally exists between the two layers of the serous pericardium. It is when this fluid accumulates in the pericardial space that the pericardial effusion can become pathologic. The production of fluid is balanced by the corresponding absorption of fluid by lymphatic channels. The parietal pericardium is drained by the anterior and posterior mediastinal lymph nodes; visceral pericardium is drained via the tracheal and bronchial lymph nodes.[16] Pericardial mesothelial cells contain dense microvilli that facilitate ion and fluid exchange.[17] Effusions arise when production exceeds reabsorption. Thus, effusions can arise from either overproduction or from underabsorption.

### Clinical Features

A wide spectrum of clinical presentations exists for pericardial effusions. Many are asymptomatic and found incidentally by ECHO, this is especially true for elderly women.[18] On the other end of the spectrum are those patients presenting in cardiac tamponade.

Symptoms of pericardial effusions may include dyspnea, fever, chest pain, or hemodynamic instability. Signs include a pericardial friction rub, EKG abnormalities, or pulsus paradoxus (described in cardiac tamponade section).

Posner et al. found that the initial presentation of cardiac tamponade was suggestive of malignancy, especially with very large effusions. Fever, pericardial friction rub, and improvement after starting nonsteroidal anti-inflammatory drugs are suggestive of idiopathic pericardial effusion.[19] In 60 percent of patients, a known previous condition that could cause a pericardial effusion was present. The underlying condition was the cause in greater than 90 percent of these patients. The presence of inflammatory signs (chest pain, pericardial friction rub, fever, or EKG changes) was predictive for acute idiopathic pericarditis. Furthermore, a large effusion without tamponade or inflammatory signs was predictive of chronic idiopathic effusion. Tamponade without inflammatory signs was predictive of malignancy.[20]

### Diagnostic Modalities

Before the advent of ECHO, the diagnosis of a hemodynamically significant pericardial effusion was difficult and needed to be confirmed by physical exam. ECHO is now considered the gold standard for diagnosis of effusions (Fig. 47-2) and can help confirm the diagnosis of a hemodynamically significant effusion (tamponade). Importantly, a "negative" ECHO does not eliminate the possibility of tamponade. Cardiac catheterization can aid in the diagnosis of tamponade or pericardial constrictive disease, but does not impact the diagnosis of effusion.

Attention must be drawn to specific ECHO findings. Some patients with evidence of right atrial and ventricular collapse have no clinical evidence of tamponade. Levine et al.[21]




**FIGURE 47-2** Large pericardial effusion detected on echocardiogram. Note the large nonechogenic (dark) fluid-filled space around the entire heart.

performed right-sided heart catheterization and pericardiocentesis on a group of patients with ECHO evidence of tamponade. Many patients had no hemodynamic evidence of tamponade. Systolic blood pressure was greater than 100 mm Hg in 94 percent. Pulsus paradoxus was present in only one-third of patients. Right atrial collapse had a positive predictive value of only 50 percent.

## Treatment

### MEDICAL THERAPY

The success of medical therapy for pericardial effusions depends on the underlying disease processes that cause the effusion to occur. If systemic signs of inflammation are present, a course of nonsteroidal anti-inflammatory agents or steroids should be started, unless evidence of hemodynamic compromise is suspected. Any underlying infection should be treated if known.

Medical therapy is most useful with malignant effusions. Chemotherapy or radiotherapy may be useful in preventing recurrence after aspiration of the fluid. Vaitkus et al. report a success rate of 78 percent in preventing recurrence after systemic chemotherapy was given. Radiation therapy also had good results, especially with radiosensitive tumors such as lymphoma, with success rates greater than 90 percent. Instillation of sclerosing agents (e.g., tetracycline or bleomycin) through an indwelling catheter also reduced recurrence in some small series.[22]

### SURGICAL THERAPY

Surgical therapy of pericardial effusion consists of pericardiocentesis with or without catheter placement, pericardial window, and pericardiectomy. The indications and techniques will be described.

Pericardiocentesis or other modes of surgical drainage are indicated for patients with clinical aspects of cardiac tamponade, suspicion of infection, and in patients with large idiopathic chronic pleural effusions. Pericardiocentesis or drainage is not warranted in the initial management of asymptomatic patients with a large effusion. However, when large asymptomatic effusions persist for more than 3 months, the risk of tamponade without a specific inciting event approaches 30 percent.[23]

Pericardiocentesis can be performed either in the catheterization laboratory (under fluoroscopic guidance) or at the bedside. It should be the initial therapy for those in overt tamponade when such a procedure can be easily and safely performed, and for those patients that are not in the immediate postoperative period. Once the decision is made to proceed with pericardiocentesis, the decision is to perform either simple aspiration or percutaneous catheter drainage. These authors favor the latter approach. With this approach, the subxiphoid area is infiltrated with 1 percent lidocaine for local anesthesia. An 18-gauge spinal needle is inserted to the left of the xiphoid process at a 45° angle toward the left shoulder. A "pop" is felt when the needle enters the pericardial sac. This can be aided with either fluoroscopic or ECHO guidance. An 8F pigtail catheter is then placed in the pericardial space using the Seldinger technique. Fluid should be aspirated and then sent for culture and cytology. If blood is withdrawn, it is placed in a small basin and observed. Clotted blood suggests that a cardiac chamber was entered. If ECHO is being used for guidance, a simple bubble study can be used to verify extracardiac positioning of the catheter needle. A follow-up CXR evaluates catheter placement and any evidence of pneumothorax. Techniques have also been described using an alligator clip attached to the needle and one lead of the EKG. When the myocardium is violated with the needle, a deflection will be noted on the EKG.

Pericardial drainage can also be achieved by creating a pericardial window. Surgical approaches include subxiphoid, left anterior thoracotomy, or thoracoscopy (VATS). General anesthesia is preferred for all approaches. Especially when tamponade is the presumptive diagnosis, the patient should be prepped and draped prior to induction of anesthesia since hypotension and hemodynamic instability may ensue, and rapid drainage may be necessary.

The subxiphoid approach consists of a 6- to 8-cm incision that starts at the junction of the sternum and xiphoid. The xiphoid process is either resected or split. An Army–Navy retractor is placed under the sternum. Dissection is continued under the sternum until the pericardium is identified and incised. The fluid is drained and sent for culture and cytology. The largest possible piece of pericardium is resected and any intrapericardial loculations are broken with finger dissection. A 28F right-angled chest tube is placed into the pericardial space through a separate stab incision. The surgical pericardial incision can be closed, left opened, or drained into the peritoneal space.

Pericardial drainage can be approached by left anterior thoracotomy. A double-lumen tube is not necessary for this approach. A small roll should be placed under the patient's left shoulder, so that the patient is at a 30° angle from the table. A 6- to 8-cm incision is made in the infra-mammary crease with the nipple as its most medial aspect. Subcutaneous dissection is continued superiorly for one rib space. The fourth intercostal space is entered; the intercostal muscles are taken off the fifth rib medially and laterally. A sponge stick is used to push the lung away. The pericardium is identified and incised. The fluid is drained and sent for culture and cytology. The pericardium is resected anterior to the phrenic nerve, with the largest possible section being taken. The incision is closed after a 28F chest tube is placed through a separate stab incision. The pericardial space can be drained directly with the chest tube, or the tube can be left in the pleural space under the assumption that any reaccumulation of pericardial fluid will drain into the pleural space.

Thoracoscopy can be used to create a pericardial window. However, this approach does require placement of a dual lumen endotracheal tube and single lung ventilation. Patients with clinical tamponade often will not tolerate this approach.

A port for the camera and two working ports are placed. The chest cavity is first inspected, including identification of the phrenic nerve. The pericardium is then incised anterior to the nerve and a large piece of pericardium is resected. Care is taken not to leave a defect so large that cardiac herniation may occur. A single 28F chest tube is left in the pleural space.

## Outcomes/Prognosis

The outcomes and prognoses for pericardial effusions relate to the underlying disease process. Patients with malignant effusions have a median survival of 2 to 3 months.[24] A recent study by McDonald et al.[25] compared subxiphoid pericardial window to percutaneous catheter placement. No direct procedural mortality occurred in either group. However, the in-hospital mortality and recurrence rates were significantly higher in the percutaneous group. Allen et al. reviewed combined results in the literature, and similar results were noted.[26] Surgical drainage had mortality, complication, and recurrence rates of 0.6, 1.5, and 3.2 percent, respectively. Catheter drainage had rates of 1.9, 10.6, and 13.8 percent, respectively. Thus, despite the relatively short-term benefit of any procedure, compared with percutaneous approaches, surgical drainage may allow more patients to be discharged from the hospital.

# CARDIAC TAMPONADE

## Epidemiology

Cardiac tamponade occurs when the increase in pericardial fluid leads to a significant rise in intrapericardial pressure, subsequently causing hemodynamic embarrassment. Etiologies include bleeding (spontaneous, traumatic, postoperative) and other sources of chronic effusions (discussed previously).

Cardiac surgeons are most familiar with cardiac tamponade in the immediate postoperative period. Series report that the overall incidence is 0 to 8 percent[27,28] following cardiac surgery. Tamponade in the postoperative period can be difficult to diagnose since typical signs and symptoms may be related to expected (or assumed) cardiac dysfunction (e.g., low output syndrome). Because of this, tamponade is a diagnosis of exclusion, but one that must be entertained early in the postoperative period for the unstable patient.

## Pathophysiology

Under normal circumstances, intrapericardial pressure is similar to intrapleural pressure, both being subatmospheric. As left ventricular volume increases by rapid infusion of blood during early diastole, intrapericardial pressure increases. Understandably, during this time the right ventricle is also filling. Since the right ventricle is thin walled, however, increases in intrapericardial pressure (or extrinsic compression from a clot) can exert a more deleterious effect upon this chamber. With tamponade, accumulation of fluid in the relatively non-compliant pericardial space (tough fibrous pericardium) causes the intrapericardial pressure to increase rapidly,. Additional increases in intrapericardial fluid result in the loss of diastolic compliance and depressed cardiac function.

As the consequences of tamponade progress, higher filling pressures are required for the ventricles to fill. Compensatory mechanisms include higher systemic and pulmonary artery pressures by vasoconstriction,[29] tachycardia, time-dependent pericardial stretch, and blood volume expansion.[30] This latter mechanism only aids in compensating for slow-growing pericardial effusions.

Intrapericardial pressure rises initially to levels greater than left and right atrial pressures with the aforementioned compensatory mechanisms occurring. When right and left atrial, right and left ventricular, pulmonary artery wedge, and intrapericardial pressures equalize, cardiovascular collapse ensues.

## Clinical Features

Cardiac tamponade presents as hypotension and/or decreased cardiac output. Venous pressures are elevated, and jugular venous distension may be present. The classic Beck's triad,[31] muffled heart sounds, elevated venous pressure, and decreased systemic arterial pressure, may or may not be present.

The cardiac surgeon encounters cardiac tamponade most often in the immediate postoperative period. Although the classic signs of tamponade (equalization of right and left heart pressures, decreased cardiac output, and hypotension) may be present, the clinical diagnosis is often more subtle. Other features can include decreased urine output, worsening acidosis, increased inotrope or pressor dependence, or new hemodynamic instability. These authors advocate prompt surgical reexploration if any of the above criteria are met and tamponade is plausible.

## Diagnostic Modalities

Physical examination may aid in making the diagnosis of cardiac tamponade. Beck's triad may be present. Jugular venous distension and pulsus paradoxus may also be present. Pulsus paradoxus is characterized by a decrease in systolic blood pressure by 10 mm Hg during quiet inspiration.[32] The mechanism results from increased caval blood flow during inspiration on the nonintubated patient. With increased venous return, right ventricular volume increases. Because of the increased pressure in the pericardial space, the septum is shifted and left ventricular volume is decreased. This translates into decreased cardiac output and arterial hypotension.

ECHO confirms the diagnosis and can confirm the size and extent of effusions. ECHO can confirm pulsus paradoxus when inspiration increases right ventricular size while decreasing left ventricular size in the presence of a large pericardial effusion. Compression of the right ventricular free wall during late diastole–early systole lasting more than one-third of the cardiac cycle is a sensitive sign. Right ventricular indentation during early diastole is more specific.[33] One must remember that tamponade is not an all-or-none phenomenon. The use of ECHO in the immediate postoperative period can be problematic. Transthoracic views can be limited by chest tubes or dressings. Immediately postoperatively, some degree of effusion always exists. Although ECHO may give you the diagnosis of tamponade, it does not rule out tamponade. We abide by the dictum that postoperative cardiac tamponade is a clinical, not echocardiographic, diagnosis.

## Treatment

### MEDICAL THERAPY

Very little medical therapy exists for cardiac tamponade. The mainstay consists of volume expansion to optimize preload while procedural intervention is planned.

### SURGICAL THERAPY

Surgical therapy for cardiac tamponade depends on the circumstances in which tamponade arises. The goal of surgical therapy is two-fold: relieve extrinsic cardiac compression and reverse the inciting event. Surgical therapy for pericardial effusions with tamponade physiology was discussed in the previous section.

In the postoperative period, sternal reentry is the approach of choice. Careful attention should be focused on the specific location of clot. For example, thrombus around the aorta should lead the surgeon to the aortic cannulation site or proximal anastomoses as potential sources for bleeding. Nevertheless, complete exploration and verification of all surgical sites is paramount. Aggressive correction of any coagulopathy should also occur; this includes ensuring that the patient is warm. All too often, we forget that a cause of coagulopathy is hypothermia. Rapid infusion of cold volume can exacerbate the problem.

Cardiac tamponade from trauma poses a more difficult problem. In this setting, the surgical approach is dictated by the mode of injury. Penetrating injuries should be explored according to the direction of trajectory. Pericardiocentesis may alleviate tamponade in the emergency room until an operating room is available. When we have planned an exploration via the left chest, we have occasionally started with a subxiphoid window to eliminate blood in the pericardium prior to placing the patient in the lateral decubitus position. Left thoracotomy, median sternotomy, and clamshell incisions all provide access to the pericardium and drainage of blood. Presence of other suspected injuries should dictate which approach is taken.

# PERICARDITIS

## Epidemiology

Over the last half of the century, etiologies for pericarditis have changed. Historically, tuberculosis (TB) was the major cause of infective pericarditis. Infectious diseases now cause fewer cases of pericarditis with the emergence of other etiologies such as previous cardiac surgery, malignancy, radiation, and trauma.[34]

Infection does remain a common cause of pericarditis. Sources include the heart itself, the surrounding tissues, septicemia, and from the incision in postoperative patients. Sources can be both bacterial and viral. As expected, infections are much more serious in immunosuppressed patients such as transplant and AIDS patients. Viral pericarditis is usually mild and self-limiting and may in fact be subclinical. On the other hand, acute bacterial pericarditis can be life threatening. The most common agents of bacterial pericarditis are streptococcus, pneumococcus, and staphylococcus.[35] Although now less common now, TB remains an etiology, especially in the immunocompromised patient. The pathologic stages seen in tubercular pericarditis are characterized by fibrinous exudation followed by serosanguinous effusions. These resorb and organize into caseating granulomas, pericardial thickening, fibrosis, and constriction.[36]

Pericarditis can be seen in renal failure patients, either due to infection (from dialysis access for example), their relative immunosuppressed state, or from uremia. Although the exact etiology of uremic pericarditis is unknown, nitrogen retention is required for its development. This condition was first described by Bright in 1836.[37]

A few drugs are classically associated with pericarditis. These are procainamide, hydralazine, methylsergide, emetine, and minoxadil.

Other metabolic causes of pericarditis include systemic lupus erythematosus (SLE), hypothyroidism, and rheumatoid arthritis (RA). Approximately one-half of patients with RA have pericardial effusions or pericardial adhesions. Patients with more severe RA tend to have worse pericardial issues, thought to be related to the deposition of immune complexes in the pericardium.[38]

Radiation is the most common cause of constrictive pericarditis in the United States,[39] and is dominant in part from an era when mediastinal irradiation was a common form of treatment for lymphoma. Postmastectomy irradiation as well as treatment of some lung cancers also contributes. The degree of inflammation and subsequent constriction relates to the total dose of radiation. One series reported that over 20 percent of patients with radiation-induced pericarditis ultimately require pericardiectomy.[40]

Trauma, cardiac surgery, and myocardial infarction account for additional causes of pericarditis. Both blunt and penetrating trauma can result in pericarditis as a sequelae to even a small, bloody pericardial effusion. Approximately 50 percent of patients that have had a transmural myocardial infarction develop pericarditis, known as Dressler's syndrome. Constrictive pericarditis can result from cardiac surgery, but this occurs in less than 5 percent of patients.[41]

## Pathophysiology

Pericarditis by definition is an inflammation of the pericardial sac. The degree as well as extent of inflammation will vary from patient to patient, as will the subsequent events following this inflammation. For pathological pericarditis (i.e., resulting in constrictive pericarditis) the basic premise is that inflammation leads to scar and fibrosis (Fig. 47-3). This, in turn, leads to constriction and the pathophysiologic processes described below.

The sine qua non of constrictive pericarditis is limitation in cardiac filling. The atria serve three functions: a conduit, a reservoir, and a pump. The primary function is that of a conduit and contributes to the rapid early filling of the ventricles during diastole. The majority of diastolic filling occurs in early diastole. This process of filling becomes abnormal when the distension of the ventricles is limited by the fibrous pericardium. Pressures within the heart chambers are relatively normal until the distention of the ventricles becomes limited. End diastolic pressures suddenly increase, manifested by the "square root" sign seen on ventricular pressure tracings during cardiac catheterization.

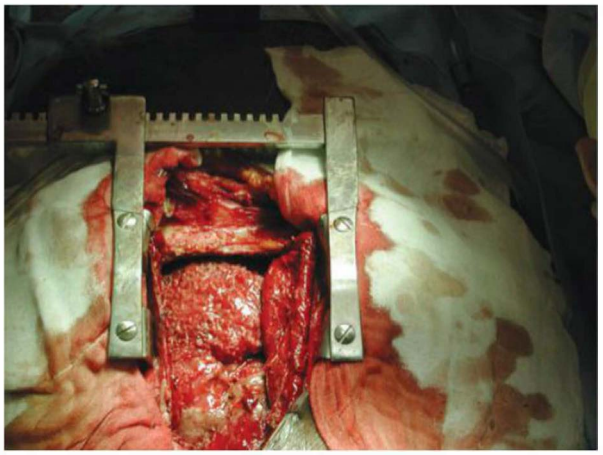


**FIGURE 47-3** Fibrinous pericarditis. Note the characteristically thickened walls of the opened pericardial sac and the intrapericardial adhesions. (Reproduced with permission from Abe DeAnda Jr., MD.)

## Clinical Features

Clinical findings depend on the severity of constriction. Patients with mild constriction may be asymptomatic. As constriction becomes more severe, signs and symptoms of heart failure become more pronounced; the heart failure may be limited to one side or biventricular. Venous pressures become higher and symptoms of right-sided heart failure become more prominent. Early symptoms include jugular venous distension, hepatomegaly, and peripheral edema. As symptoms progress, ascites, worsening peripheral edema, and pleural effusions may develop.

## Diagnostic Modalities

A few signs may be present with constrictive pericarditis. During inspiration, jugular venous distension may worsen; this is the so-called Kussmaul's sign. Pulsus paradoxus may also be present. A prominent S3 heart sound may be heard. This pericardial knock is secondary to the rapid ventricular filling during diastole. Murmurs are often absent.

Basic studies such as CXR and ECG may be useful in pointing the clinician to the diagnosis. Nonspecific ST elevation or T-wave abnormalities are present in more than 90 percent of patients. On CXR, pericardial calcification is seen in 40 percent of patients.[42] Computerized tomography (CT) can demonstrate a thickened pericardium (Fig. 47-4). Isolated findings must be supported by physiologic criteria. Another modality is MRI, which is more sensitive and specific than CT in the diagnosis of constrictive pericarditis. MRI can show right atrial dilatation and

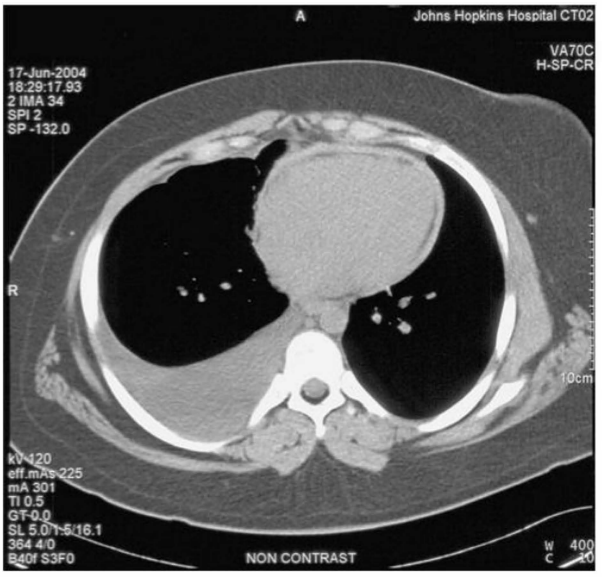



**FIGURE 47-4** Computed tomogram of revealing thickened pericardium consistent with constrictive pericarditis.

right ventricular compression. Pericardial thickness greater than 4 mm by MRI is suggestive of constriction in patients with appropriate clinical presentation. MRI can also show variations in respiratory-related filling, suggesting constriction.[43] The sensitivity and specificity of MRI is greater than 90 percent.[44]

ECHO can be useful in constrictive pericarditis. The initial role of 2-D ECHO can exclude other causes of right-sided heart failure. Pericardial thickening can be seen but is not diagnostic. Displacement of the interatrial septum toward the left atrium during inspiration and septal bounce are suggestive of pericardial constriction. M-mode Doppler can show signs of rapid early diastolic filling, ventricular interdependence, and increased right-sided diastolic pressure. All are signs of pericardial constriction.[45] Tissue Doppler imaging is a newer echocardiographic technique that can aid in making the diagnosis of constriction and has a high sensitivity (82.5 percent) and specificity (92.7 percent) in differentiating constrictive pericarditis from controls.[46]

Right and left heart cardiac catheterization remains the gold standard in the diagnosis of constrictive pericarditis. Hallmark features include equalization of end-diastolic pressures in the right atrium, left atrium, and pulmonary artery. Right and left ventricular pressures are also equalized.[47] Mean atrial pressures should be above 10 mm Hg on the right and left side of the heart. The "square root" sign, described earlier, is seen on ventricular tracing during catheterization (Fig. 47-5). The right atrial tracing demonstrates a prominent Y descent. The left ventricular ejection fraction should be greater than 40 percent. RVEDP is elevated and should be greater than one-third of RV systolic pressure. This finding has 95 percent sensitivity for the diagnosis of constrictive pericarditis.[48]

The clinician often has difficulty differentiating restrictive cardiomyopathy from constrictive pericarditis. Making the diagnosis is critical because constrictive pericarditis can be surgically cured. Transplantation is the only surgical treatment for restrictive cardiomyopathy. The above criteria are neither very sensitive nor specific to aid in making this distinction. Criteria suggestive of restrictive cardiomyopathy include the following: small- or normal-sized heart, reduced left ventricular function, pulmonary and hepatic congestion, and prominent X and Y descents on atrial tracing. Yet, none of these is pathognomonic.

Ventricular interdependence is the most sensitive and specific test for constrictive pericarditis. This is observed during cardiac catheterization. During the respiratory cycle, concordant increases in right and left ventricular pressure are expected with inspiration. With constrictive pericarditis, discordance is seen. This observation has a sensitivity of 100 percent and a specificity of 95 percent.[49]

When the diagnosis remains unclear after cardiac catheterization, more invasive means can be used to aid in making the diagnosis. Endomyocardial biopsy may be useful. If it is normal or there are mild inflammatory changes, biopsy does not help in distinguishing restrictive from constrictive pericarditis. Findings of amyloid are diagnostic for restrictive cardiomyopathy. Shoenfeld et al. found that the diagnosis of restrictive cardiomyopathy was made on biopsy in 39 percent of patients when the diagnosis was unclear after less invasive testing.[50]

When all other modes of testing fail, the diagnosis can be made by mini exploratory thoracotomy. If no pericardial pathology is present, the patient is closed. If constrictive pericarditis is found, formal pericardectomy is done.

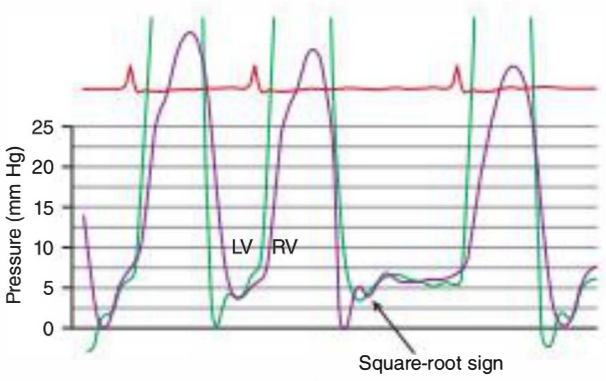



**FIGURE 47-5** Square-root sign in right ventricular pressure tracing in constrictive pericarditis. (Modified with permission from Spodick DH (ed). *The Pericardium: A Comprehensive Textbook*. New York: Marcel Dekker, 1997:4.)

## Therapy

### MEDICAL THERAPY

Treatment of the underlying cause of pericarditis is the only medical therapy. However, most often the etiology is unknown. Surgical therapy remains the mainstay of treatment.

### SURGICAL THERAPY

Once the diagnosis of constrictive pericarditis is confirmed, operative intervention is employed. Many patients present with advanced heart failure. An arterial line and pulmonary artery catheter should be placed. Surgical approaches include median sternotomy, left anterior thoracotomy, or bilateral anterior thoracotomies, and will vary based on surgeon preference and patient history.

The median sternotomy approach starts in the usual manner. The cardiopulmonary bypass pump should be set up and made ready. The thymic fat pad is dissected to the innominate vein. The anterior aspect of the pericardium is palpated and inspected. A scalpel is used to incise the pericardium in the midline, starting anterior to the aorta. Care must be taken during this step as the pericardium often is densely adherent to the heart. Pericardial flaps are lifted inferiorly and laterally. The dissection over the left side of the heart may need to be done on cardiopulmonary bypass. The pericardium needs to be stripped from phrenic nerve to phrenic nerve laterally,

the diaphragm inferiorly, and the atrioventricular groove superiorly. Bands between the right ventricle and the pulmonary artery need to be excised. Failure to do so may lead to pulmonary hypertension.[51] One may need to leave islands of unstripped pericardium over the coronaries, remembering that the serous visceral pericardium is in continuity with the adventitia of the coronary arteries. The pericardium over the right atrium and cavoatrial junction does not need to be stripped, as there is no hemodynamic advantage to this and the risk of bleeding is substantial.[52]

An alternative surgical approach for performing a pericardectomy is a left anterior thoracotomy. The patient is intubated with a dual-lumen endotrachial tube. An arterial line and pulmonary artery catheter is placed. The groins should be prepped should cardiopulmonary bypass be needed. A small roll is placed under the left shoulder. The lung is deflated and the fourth intercostal space is entered through a left inframammary incision. The phrenic nerve is identified\ and the pericardium is incised anteriorly. Dissection is continued anteriorly to the right atrium, inferiorly to the diaphragm, and superiorly to the pulmonary artery.

Sometimes the dissection of the right ventricle is very difficult through this incision. The left anterior thoracotomy can be extended across the sternum to a right anterior thoracotomy (clamshell incision). This exposure is outstanding. Only rarely is cardiopulmonary bypass needed with this approach. All surgical approaches offer equal results and should be dictated by surgeon preference.

## Outcomes/Prognosis

Early mortality for pericardiectomy ranges from 5 to 10 percent, with 5-year survival ranging between 65 and 90 percent. Patients with idiopathic cardiomyopathy had the best survival (88 percent 7-year survival). Predictors of poor outcome were prior radiation, renal insufficiency, poor ventricular function, higher pulmonary artery pressures, NYHA class IV, low serum sodium, ascites, and hyperbilirubinemia.[36,53,54]

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## PERICARDIAL DISEASE BOARD REVIEW QUESTIONS (CHAPTER 47)

1. Beck's triad consists of muffled heart sounds, elevated venous pressure, and:

   A. Decreased systemic arterial pressure
   B. Friction rub
   C. Peripheral edema
   D. Fever
   E. Leukocytosis

2. The three most common etiologies for pericardial effusion include uremia, idiopathic, and:

   A. Tuberculosis
   B. Myocardial infarction
   C. Neoplasia
   D. Trauma
   E. Heart failure

3. Which modality is considered the gold standard for diagnosing pericardial effusions?

   A. Computed tomography
   B. Magnetic resonance imaging
   C. Cardiac catheterization
   D. Echocardiography
   E. Pulmonary arterial catheterization

4. Predictors of poor outcome after pericardiectomy include all but which of the following:

   A. Prior radiation
   B. Renal insufficiency
   C. Poor ventricular function
   D. NYHA class IV symptoms
   E. Hypernatremia

5. Hallmark features for constrictive pericarditis include all but which of the following:

   A. Equalization of end-diastolic pressures in the right atrium, left atrium, and aorta
   B. Equalization of right and left ventricular pressures
   C. "Square-root" sign on ventricular tracings during catheterization
   D. Elevated right ventricular end-diastolic pressure (RVEDP) that is greater than one-third of the right ventricular systolic pressure
   E. Equalization of end-diastolic pressures in the right atrium, left atrium, and pulmonary artery.

## ANSWERS

1. **Answer: A.** Beck's triad consists of muffled heart sounds, elevated venous pressure, and decreased systemic arterial pressure. Although a friction rub, peripheral edema, fever, and leukocytosis can be associated with pericarditis and/or a pericardial effusion, they are not components of Beck's triad.
2. **Answer: C.** The three most common etiologies for pericardial effusion include uremia, idiopathic, and neoplasia. Myocardial infarction, trauma, and heart failure are also etiologies for pericardial effusion, but not as common statistically. Tuberculosis is now an uncommon cause of pericardial effusion.
3. **Answer: D.** Echocardiography is considered the gold standard for diagnosing pericardial effusions. Although computed tomography, magnetic resonance imaging, cardiac catheterization, and pulmonary arterial

catheterization can also visualize and/or aid in the diagnosis of pericardial effusions, echocardiography does not use ionizing radiation and also demonstrates the functional manifestations of hemodynamically significant effusions (e.g., right ventricular chamber collapse).

4. **Answer: E.** Predictors of poor outcome after pericardiectomy include prior radiation, renal insufficiency, poor ventricular function, NYHA class IV symptoms, hyponatremia, ascites, and hyperbilirubinemia. Hypernatremia is not an identified predictor of poor outcome after pericardiectomy.
5. **Answer: A.** Hallmark features for constrictive pericarditis include equalization of end-diastolic pressures in the right atrium, left atrium, and pulmonary artery, equalization of right and left ventricular pressures, and the "square-root" sign on ventricular pressure tracings. Elevation of RVEDP has a 95% sensitivity for the diagnosis of constrictive pericarditis.

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# 48 Primary Cardiac Tumors

*Brian T. Bethea*
*Adam Richter*

**KEY CONCEPTS**

- Epidemiology
  - Primary cardiac tumors are rare with an overall incidence of 0.02 percent. Malignant tumors metastatic to the heart are much more common with an incidence of 1.23 percent. About 25 percent of primary cardiac tumors are malignant (made up mainly of sarcomas), and about 75 percent are benign. Myxomas make up about 50 percent of benign cardiac tumors.
- Pathophysiology
  - Cardiac tumors arise from various cells in the heart. Clinical effects of these tumors are based chiefly on the size and location of the mass. Tumors can cause obstruction of valvular orifices as well as incompetence of valve leaflets, leading to symptoms of obstruction and congestive heart failure. In addition, friable tumors can embolize, causing systemic effects.
- Clinical features
  - The most common presentation of cardiac tumors is evidence of congestive heart failure due to obstruction and/or valvular insufficiency. Signs and symptoms of embolization include myocardial infarction, stroke, peripheral malperfusion, and mesenteric ischemia. Constitutional symptoms such as malaise, weight loss, myalgias, and fevers can occur due to elaboration of cytokines. Other presenting signs and symptoms can include arrhythmias, sudden death, chest pain, and pericardial tamponade.
- Diagnosis
  - A chest x-ray and electrocardiogram can suggest large tumors or those causing conduction disturbances. The mainstay of diagnosis, however, is echocardiography. Transthoracic echocardiography is an excellent screening tool, but transesophageal echocardiograaphy can provide higher resolution and more information about the dynamic effects of the mass during the cardiac cycle and the precise location of the tumor. Computed tomography (CT) scan and magnetic resonance imaging (MRI) are also useful in further characterizing cardiac masses and determining the depth of invasion in cases of malignant lesions.
- Treatment
  - The mainstay of treatment for the vast majority of cardiac tumors is surgical excision. Resection should be performed as quickly as possible after diagnosis given the risk of systemic embolization. Sarcomas portend a poor prognosis, but survival can be improved with surgical resection when technically feasible. In addition, some studies have suggested that chemotherapy and radiation therapy may enhance survival. Treatment of primary cardiac lymphomas is centered on chemotherapy with surgery only used for palliative debulking.
- Outcomes and prognosis
  - The prognosis of resectable benign tumors is usually very good with low recurrence rates depending on the type of tumor. In contrast, the prognosis of malignant lesions is dismal with the median survival being only 6 to 18 months, even with surgical resection or transplant.

## INTRODUCTION

### Definitions

Primary cardiac tumors are classified as neoplastic, hamartomatous, or hyperplastic. Typically, cardiac tumors originate from one of the following cell lines: mesenchymal, endothelial, neuroconduction system, autonomic nerve tissues, lymphatic tissues, or any other cell types normally found in the heart. Only tumors arising from cells within the myocardium and endocardium will be discussed in this chapter; masses arising from the pericardium will not be addressed.

## History

The first known documentation of a cardiac tumor was by Realdo Colombo in his studies of anatomy in 1559.[1] By 1865, both benign and malignant cardiac tumors had been described, including fibromas, rhabdomyomas, and sarcomas. It was not until 1952, however, that the first report of a premortem diagnosis of atrial myxoma was published. The first successful surgical resection of a myxoma followed in 1954.[2] Currently, echocardiography and other imaging modalities allow for the rapid and accurate diagnosis of cardiac tumors. Furthermore, sophisticated operative techniques for resection and subsequent reconstruction are well established.

## Overview

Cardiac neoplasms represent a rare disorder of the heart. Based on autopsy studies, the incidence of primary cardiac tumors is estimated to be 0.02 percent (ranging from 0.0017 to 0.25 percent).[3] Metastatic tumors to cardiac structures are more common than primary tumors with an estimated incidence of 1.23 percent in a large autopsy study. Common metastatic lesions include carcinoma of the lung, esophagus, breast, liver, melanoma, and lymphoma.[4,5] Regarding primary cardiac tumors, it is generally accepted that three-quarters are benign and one-quarter are malignant.[3] Among the benign tumors, atrial myxomas are by far the most common, accounting for one-half of all benign cardiac tumors, with other less common tumors being papillary fibroelastomas, lipomas, and rhabdomyomas. The most common malignant cardiac tumors are sarcomas.

Due to their relative infrequency, the diagnosis of cardiac neoplasms can be challenging. Clinical manifestations are independent of the pathologic subtype and are usually a function of the location of the tumor, propensity for systemic embolization, or nonspecific constitutional symptoms caused by elaboration of cytokines by the tumor. For example, patients may present with symptoms of either right- or left-sided heart failure secondary to the location and point of obstruction caused by the mass. Valvular masses can cause insufficiency or relative stenosis of the affected valve, and mechanical obstruction can occur due to the shape of the mass and its ability to occlude the valvular orifices, the vena cavae, or inflow from the pulmonary veins. Furthermore, left-sided masses can embolize to the systemic circulation, causing cerebrovascular events, myocardial infarction, and end-organ or limb malperfusion. Echocardiography is the initial diagnostic test of choice; however, EKG-gated computed tomography (CT) and magnetic resonance imaging (MRI) can provide useful additional information in terms of tumor diagnosis, extent, and involvement.

Treatment involves complete excision for curative therapy for benign tumors and even for malignant tumors when possible. The prognosis is generally excellent with benign resectable neoplasms; it remains dismal with malignant neoplasm, with survival generally around 1 to 2 years. Regardless, resection is recommended for cardiac sarcomas when feasible with adjuvant chemoradiation being protocol driven. Primary cardiac lymphomas are treated mainly with chemoradiation; surgical debulking can be performed for palliation.

# CLINICAL PRESENTATION

Cardiac tumors often present as an incidental finding on echocardiography or as a new finding during operations for other indications. Symptoms of cardiac tumors can be broken down into three general categories: cardiac manifestations, embolic phenomena, and systemic manifestations. As will be discussed in more detail, these symptoms are dependent on the location and mobility of the tumor within the heart, the propensity for systemic thrombus and/or tumor emboli, and the production of cytokines causing generalized symptoms.

## Cardiac Manifestations

Cardiac manifestations are the most common symptoms of cardiac neoplasms. The typical presentation can resemble congestive heart failure with dyspnea on exertion, peripheral edema, pulmonary edema, and orthopnea.[5] Congestive heart failure caused by cardiac tumors is usually due to mechanical obstruction related to pedunculated tumors that can obstruct the mitral valve or, less commonly, the tricuspid valve orifices. Masses that arise directly from cardiac valve tissue usually cause valvular insufficiency by preventing proper leaflet coaptation of the involved valve but may, in rare circumstances, cause valvular stenosis.

Cardiac tumors, most commonly rhabdomyomas and fibromas, can be the etiology of significant arrhythmias. The arrhythmias are usually due to involvement of the myocardium and conduction system. Tumors involving the atrial septum near the atrioventricular node can cause heart block, while masses in the ventricles can result in lethal ventricular tachycardias or fibrillation. Clinical manifestations of these arrhythmias can be anywhere along the range from palpitations, syncope, to sudden death.

Other cardiac manifestations are much less common. Angina pectoris and myocardial infarction can be a manifestation of tumor emboli. Rarely, left ventricular tumors can grow and compress any portion of the left coronary artery, causing an ischemic event as well. Pericardial effusions or tamponade may occur with hemangiomas, angiosarcomas, or lymphomas.

## Embolic Phenomena

Systemic embolization is a frequent clinical manifestation of friable tumors. The emboli can consist of fragmented tumor and/or thrombus formed on the surface of the mass. The clinical result of the embolization is a function of the vessels involved and the size of the emboli. Left-sided emboli may

travel anywhere in the systemic circulation and can present as an ischemic stroke, myocardial infarction, mesenteric ischemia, or limb malperfusion. Large tumor fragments can cause occlusion of larger arteries, including the abdominal aorta. Right-sided tumors can lead to pulmonary emboli and, if the embolic burden is large enough, pulmonary hypertension may develop. Importantly, right- or left-sided embolic events in patients with no known risk factors are cardiac in origin until proven otherwise.

One recent study found the overall rate of embolization due to primary cardiac tumors to be 25 percent. This same study found that papillary fibroelastomas, which are typically found on the mitral and aortic valves, are the most likely histological tumor type to embolize. Tumors in the left atrium or on the aortic valve have the highest embolic potential.[6] Given the relatively high risk of embolization, excision of all resectable cardiac tumors should be performed expeditiously.

### Systemic Manifestations

Constitutional symptoms such as fever, anorexia, malaise, myalgias, arthralgias, and diffuse erythematous rash can be associated with cardiac tumor. This constellation of symptoms is usually associated with myxomas and is believed to be secondary to interleukin 6 production.[7] Further, patients may be anemic or present with an increased erythrocyte sedimentation rate, C-reactive protein, and globulin levels. Notably, both the systemic manifestations and laboratory abnormalities usually resolve with resection of the mass.

### Physical Exam

The physical exam is usually nonspecific in patients with cardiac tumors. Evidence of congestive heart failure (peripheral edema, hepatomegaly, jugular venous distention, and rales) may be present. Signs of systemic emboli—pulseless extremity, neurologic deficits, abdominal pain out of proportion to exam—should be assessed in all patients presenting with a cardiac tumor. Furthermore, the diagnosis of a cardiac tumor should prompt one to consider the possibility of a distant primary with metastatic lesion to the heart. For example, malignant melanoma is one of the most common cancers metastasizing to the heart, so inspection of the skin should be carried out to locate any possible lesions.

Cardiac auscultation can reveal evidence of pulmonary edema, such as a split $S_1$ or loud $S_4$. Also, a holosystolic murmur at the apex can signify mitral insufficiency, while a new-onset diastolic rumble can be heard in the case of a tumor partially occluding the mitral valve orifice during ventricular filling. These murmurs can be heard in up to 50 percent of patients with cardiac tumors.[7] The specificity of the exam is increased when the intensity of the murmur changes with patient positioning. In addition, when a left atrial tumor prolapses through the mitral valve, a loud split $S_1$ can be heard due to delayed closure of the valve. A "tumor plop" can be also be heard, which is a small murmur heard early in diastole.[5]

## DIAGNOSIS

Echocardiography is the gold standard in the diagnosis of cardiac tumors. Transthoracic echocardiography should be the initial imaging modality and usually provides all necessary information. Transesophageal echocardiography, however, is utilized if questions remain after the transthoracic echo, is especially useful with smaller tumors, and can provide greater detail regarding the size, location and even the likely point of origin of the tumor. CT and MRI are especially useful with malignant and metastatic tumors and can be used to further characterize the nature and location of cardiac masses. Other adjunctive tests, such as plain chest radiography and electrocardiography, are used in the workup of cardiac tumors to assess associated pathology and conduction abnormalities, respectively.

### Electrocardiography

Electrocardiograms should be obtained in the workup of cardiac masses to assess for rhythm disturbances. Tumors involving the conduction system or atrioventricular node can cause atrioventricular block or supraventricular tachycardias. Masses found in the ventricles, such as fibromas, can cause lethal ventricular fibrillation or tachycardia as well. Despite these concerns, most patients with cardiac tumors maintain a normal sinus rhythm.

### Chest X-Ray

A plain chest film, while not specific for cardiac tumor, is an important part of the initial workup. Significant findings on chest x-ray are cardiomegaly due to either heart failure or the mass itself, compensatory hypertrophy/dilation secondary to valvular dysfunction, or enlargement of one of the cardiac chambers from a large mass. Additional notable findings include pulmonary edema secondary to congestive heart failure and additional lesions in the lungs or bone that suggest additional metastatic disease.

### Echocardiogram

Echocardiography, either transthoracic or transesophageal, is the mainstay of the diagnosis and evaluation of cardiac tumors. Transthoracic echocardiography is easy to perform, widely available, and can be used for screening in high-risk patients, such as those with a history of previous cardiac mass or the Carney complex (described later). While transthoracic echocardiography is excellent for determining the presence of a mass, transesophageal echocardiography can give more information regarding the location of the mass, the presence and morphology of a stalk, and the precise origin of the tumor. One advantage of echocardiography is the ability to give temporal as well as spatial resolution, thus evaluating

the motion of a pedunculated tumor in the cardiac chamber and its effect on normal contraction, valvular function, and blood flow during the cardiac cycle.

## Computed Tomography

With the advent of ECG-gated CT, this modality is being used more frequently to further characterize cardiac tumors. CT can detect areas of heterogeneity, calcification, or enhancement with contrast (important in the diagnosis of hemangiomas) and can yield information with regards to the amount of myocardial involvement. This is especially important in differentiating benign from malignant disease and aids in preoperative planning.

## Magnetic Resonance Imaging

MRI can provide information regarding the anatomic location of the mass as well as the extent of invasion of the cardiac wall or septum. MRI can give better resolution of the soft tissues, thus making it more effective at determining the extent of involvement of the cardiac walls. This can be invaluable in the evaluation of masses and the differentiation between benign and malignant lesions, thus obviating the need for open biopsies. Images taken real time can also give an impression of the functional disturbances caused by the mass.[5]

## Cardiac and Coronary Angiography

In the past, angiography was used to diagnose intracardiac tumors, but the use of angiography has declined dramatically with the widespread use of echocardiography and the recognized risk of tumor fragmentation due to the angiography catheter (Fig. 48-1). Coronary angiography should be considered in all patients undergoing cardiac mass resection to determine the presence of coronary artery disease and the need for simultaneous coronary bypass. Coronary angiography can also show if a tumor derives its vascular supply from a main coronary artery, which could suggest that a bypass of that artery may be necessary.

# BENIGN TUMORS

## Myxoma

Atrial myxomas comprise one-half of all benign primary cardiac tumors, far outnumbering any other tumor type. Approximately 75 percent arise from the left atrium, with the majority originating at the edge of the fossa ovalis. An additional 15 to 20 percent arise from right atrium, again largely at the edge of the fossa ovalis. Biatrial myxomas have been described; they likely represent tumor extension from one atrium to another through the foramen ovale. The final 3 to 4 percent of myxomas arise from the ventricles with bilateral ventricular involvement being extremely rare.[7] Most myxomas arise as solitary lesions but multifocal disease has been reported. When they do arise, the majority of cases of multiple myxomas are associated with a familial myxoma syndrome, such as the Carney complex of cardiac myxoma, adrenocortical tumors, and skin hyperpigmentation. Myxomas have little to no malignant or metastatic potential, although some rare cases of metastatic myxomas have been reported.[8]

## Epidemiology

Although myxomas have been reported in people of any age ranging from infancy to 95 years, the median age at diagnosis is 50, with the majority of cases being discovered in the third through sixth decades of life.[7,9] There is a clear female preponderance, with women making up about two-thirds of diagnosed patients.[9]

The vast majority of myxomas are sporadic, but 5 to 10 percent of cases demonstrate familial patterns of inheritance. These patients are more likely to have multicentric disease, recur after excision, occur in younger patients (mean age of 23.9), and are more likely to affect males with a male-to-female ratio of 2:1.[10,11] Originally described as the NAME (nevi, atrial myxoma, myxoid neurofibromata, ephelides) and then the LAMB (lentigines, atrial myxoma, mucocutaneous, and blue nevi) syndromes, the Carney complex describes the close association of cardiac myxoma, Cushing syndrome secondary to pigmented nodular adrenocortical dysplasia, cutaneous myxoma, myxoid mammary fibroadenoma, and pigmented spots on the skin. Genetic studies have determined that the Carney complex is due to a mutation at the chromosome 17q24 locus. This locus contains the PRKAR1A gene, which codes for the R1-α regulatory subunit of the cAMP-dependent protein kinase A. Nonsense or frameshift mutations of this gene result in decreased R1-α protein; how this contributes to tumorigenesis has not yet been elucidated. Of note, it was initially thought that a mutation on chromosome 2p was the source of the symptoms in one family studied, but further analysis demonstrated that this kindred had a mutation at the 17q24 locus as well.[11] This disease is inherited with an autosomal dominant pattern.

Given that patients with familial myxoma have an elevated recurrence rate of 12 to 22 percent, close follow-up with echocardiography is recommended.[7] First degree relatives of patients with the Carney complex should be screened for cardiac myxomas.

## Pathology

Macroscopically, myxomas fit into two categories based on their gross appearance: solid and gelatinous (Fig. 48-2A and B). Solid tumors appear firm and are usually pedunculated and located on the edge of the fossa ovalis. Gelatinous tumors appear softer and more friable with clear pink or green coloration. Gelatinous tumors also have a villous or lobed

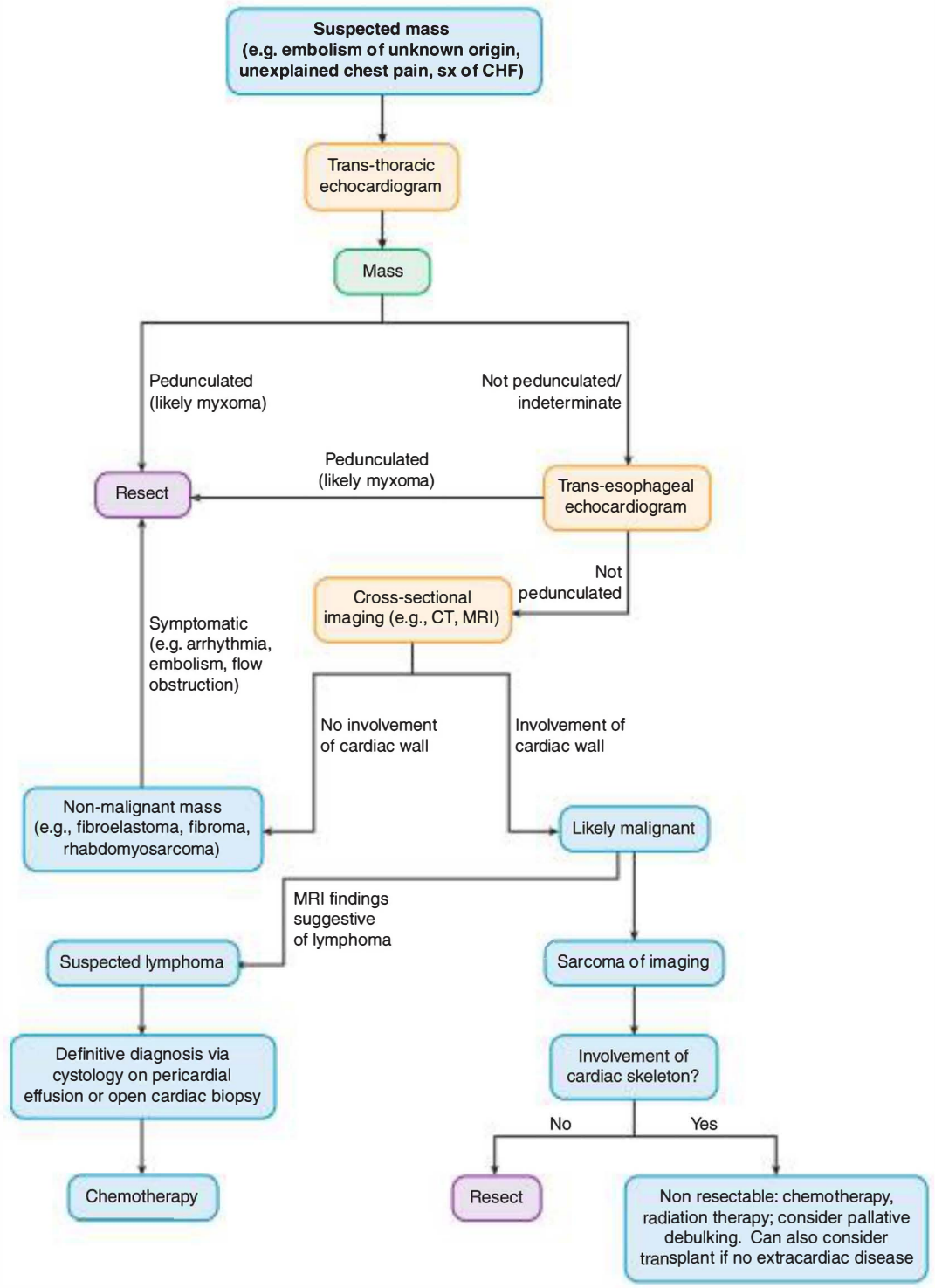



**FIGURE 48-1** Flow diagram describing the general workup and treatment of cardiac tumors.

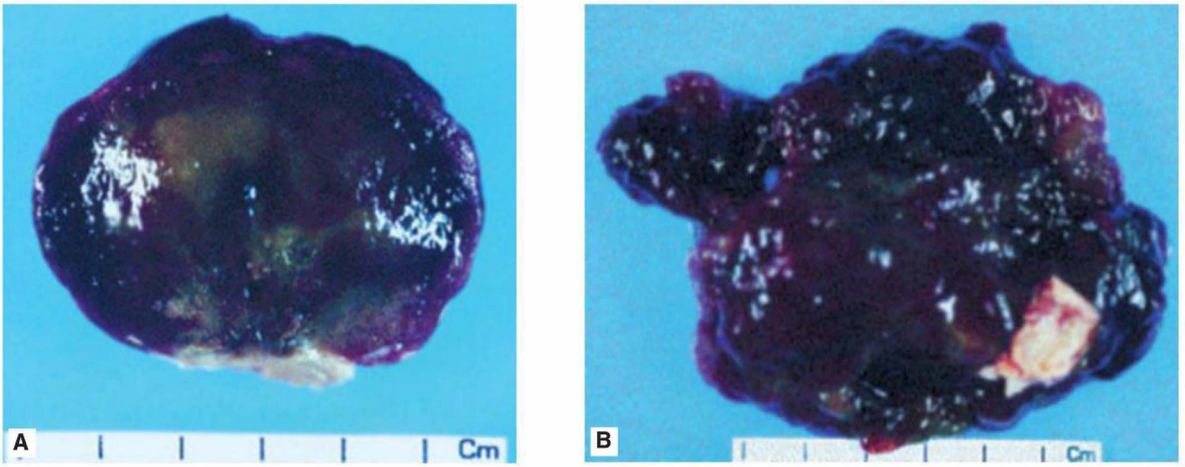



**FIGURE 48-2** Gross photographs of the two subtypes of atrial myxoma. Note the smooth, round edges in **A** as compared with the irregular, polypoid appearance of the tumor in **B**. The incidence of systemic embolism is higher with the polypoid subtype. (Reprinted from Ha JW, Kang WC, Chung N, et al. Echocardiographic and morphologic characteristics of left atrial myxoma and their relation to systemic embolization. *Am J Cardiol* 1999;83(11):1579–1582. With permission from Elsevier.)

appearance with thrombus development between the villi. These differences are not absolute, as some myxomas have characteristics of both types.[12] The clinical presentations can differ between the two, as solid tumors are more likely to present with symptoms of congestive heart failure and gelatinous tumors are more likely to embolize. These morphological differences can be seen on echocardiography.[13]

## Histology

Microscopically, myxoma cells are spindle-shaped with round or oval nuclei, prominent nucleoli, and extremely rare mitotic figures. Some cells are noted to have two nuclei. They are arranged in groups around capillaries within a myxoid stroma and can resemble endothelial cells. Also present are chronic inflammatory cells and hemosiderin-laden macrophages.[12] Areas of hemorrhage are common in both types of myxoma, but they are more common in solid tumors.[14] Necrosis and calcifications can be seen as well, up to 8.7 and 16 percent, respectively, in a study of 80 atrial myxoma resections performed at the Mayo Clinic. Other uncommon findings include bone and cartilage formation and glandular formations, including goblet cells and groups of cuboidal and columnar cells.[15]

The histogenesis of myxomas remains controversial. Initial hypotheses held that the myxomas actually arose from clot and represented highly organized thrombi. This view has largely been abandoned in favor of a neoplastic theory, although no definite progenitor cell has been implicated. Some studies have suggested that the tumors are endothelial in origin, supported by the fact that some cells will test positive for Factor VIII; it has been shown that only the cells lining vessels within the tumors have such staining properties. Presumably, these cells represent normal endothelium within the tumor and not neoplastic cells. The myxoma cells all stain strongly for vimentin, which suggests a mesenchymal origin. Also of note, many of the cells stained for S-100, a protein found in malignant melanoma as well as cells with chondromatous differentiation. Elements of smooth muscle have also been seen in myxomas; these are also located around vessels within the tumors and not dispersed within the myxomatous matrix. This has led investigators to conclude that myxomas likely arise from multipotent mesenchymal cells that may be embryological remnants.[16] An alternative hypothesis is that myxomas are actually hamartomatous in nature, rather than neoplastic (Fig. 48-3A and B).

## Treatment

The treatment of atrial myxomas is surgical excision and, in general, resection is curative. The finding of an atrial myxoma is an indication for surgery and should be done in an expedited elective fashion in order to minimize the risk of interval embolic events. The surgical approach is through a median sternotomy incision. Moderate hypothermia is used, and the patient is placed on bicaval cardiopulmonary bypass. Left atrial and ventricular myxomas are generally approached through the left atrium and right-sided lesions are approached through the right atrium. Alternatively, a transeptal approach has been advocated for left atrial myxomas, providing excellent exposure, and certainly should be the preferred approach for biatrial myxomas. Further, the transseptal approach has been reported to be associated with a reduced risk of postoperative arrhythmias.[14] Regardless of approach, most important is complete excision of the myxoma with a cuff of normal endocardium to decrease

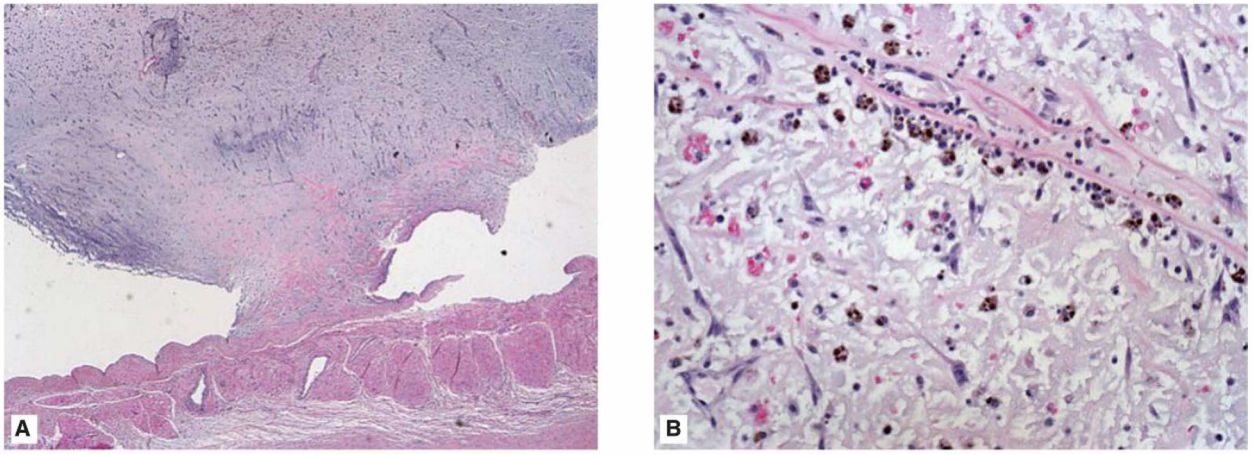



**FIGURE 48-3** Microscopic images of atrial myxoma. Note the stalk arising from the endocardium in **A**. **B** shows an area of remote hemorrhage with hemosiderin-laden macrophages. (Courtesy of Dr. Jonathan Baker, Department of Pathology, University of Texas Southwestern Medical Center.)

the chances of recurrence. The resulting defect is closed primarily if possible or patched with autologous or bovine pericardium. Lastly, all four chambers and valves should be inspected for metasychronous lesions before closing.

## Outcomes

The prognosis after complete myxoma resection is excellent, with the expected survival equivalent to that of the general population. Recurrence has been estimated to be about 3 percent in sporadic cases, but one recent study revealed a recurrence rate of up to 13 percent. Of note, this study did not differentiate between familial and de novo disease.[17] Recurrence has been has been thought to result from residual disease stemming from inadequate resection, concurrent disease undetected at the time of operation, or a subsequent separate tumorigenic event. As a result, postoperative screening with echocardiography is recommended, especially in patients with familial disease.

## Papillary Fibroelastoma

Cardiac papillary fibroelastomas or fibroelastic papillomas comprise approximately 10 percent of all benign primary cardiac tumors, although it has been suggested that they may be greatly underdiagnosed.[3,17] The vast majority arise on the aortic and mitral valves with the most common nonvalvular location being the left ventricle. Given their propensity for cardiac valves, these tumors make up about three-quarters of all valvular tumors. Multiple tumors are uncommon, but occur in up to 6 percent of patients, according to one large study.[18]

The majority of papillary fibroelastomas are found incidentally during echocardiography or at the time of surgery for other indications. When the tumors become symptomatic, the presentation is usually due to systemic embolization. Interestingly, pathologic examination of emboli in patients with papillary fibroelastoma only rarely yield evidence of the actual tumor, suggesting that the majority of embolic events are due to the dislodgement of associated thrombus. The location of the tumor is related to the symptoms and associated complications, with aortic valve tumors being more likely to cause myocardial infarction or sudden death and mitral valve tumors more commonly associated with systemic or cerebral embolic events.[19] Patients can also present with symptoms of congestive heart failure due to valvular stenosis or, less commonly, insufficiency due to interruption of the leaflets by tumor. As previously mentioned, sudden death occurs from complete obstruction of a valvular orifice or coronary artery occlusion from either aortic valve tumors adjacent to the ostia of the coronary arteries or embolic events to the coronary arteries.

## Epidemiology

Cardiac papillary fibroelastomas have been reported in patients of all ages from neonates to the elderly, but the frequency is highest in the fourth through eighth decades with a mean age at diagnosis of 60. Males have a higher incidence. No familial patterns of disease have been reported although a small number of cases have been found to be congenital. The tumors are slow-growing, but they can exhibit acute increases in size due to overlying thrombus formation.[18]

## Pathology

Macroscopically, fibroelastomas are about 1 cm in size and have many frond-like projections that are evident after immersing the tumor in saline. The fronds are suspended

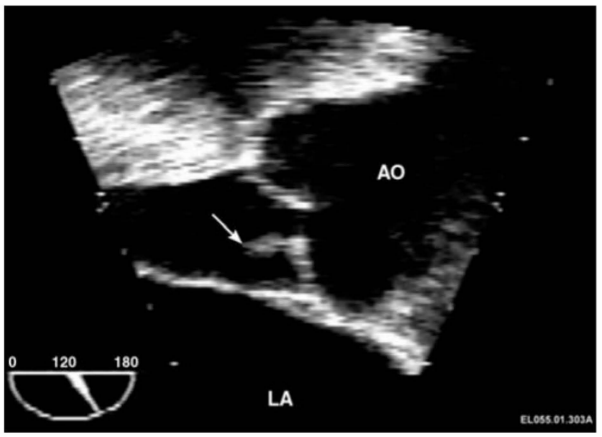



**FIGURE 48-4** Papillary fibroelastoma on the aortic valve on a long-axis view of a transthoracic echocardiogram (marked by arrow). (Reprinted from Ngaage DL, et al. Surgical treatment of cardiac papillary fibroelastoma: A single-center experience with eighty-eight patients. *Ann Thorac Surg* 2005;80:1712–1718. With permission from Elsevier.)

by a short pedicle that permits prolapse through valvular orifices (Fig. 48-4). Fibroelastomas tend to arise from the middle of the valve, rather than the edge (Fig. 48-5). This is in contrast to Lambl excrescences, which are common frond-like lesions found on the valve edges thought to represent organized thrombus due to minor endothelial damage at these sites. Fibroelastomas located on the atrioventricular valves tend to project into their respective atria, and tumors located on the semilunar valves tend to project into their respective arteries.[18]

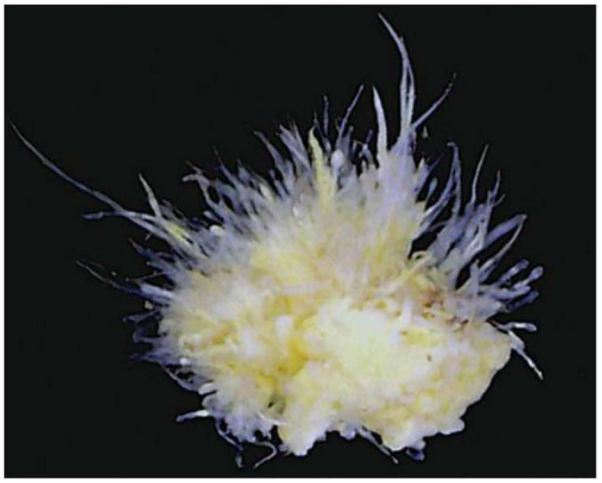


**FIGURE 48-5** Gross specimen of a papillary fibroelastoma underwater. Note the numerous fronds emanating from a central tumor. (Reprinted from Ngaage DL, Mullany CJ, Daly RC, et al. Surgical treatment of cardiac papillary fibroelastoma: A single-center experience with eighty-eight patients. *Ann Thorac Surg* 2005;80:1712–1718. With permission from Elsevier.)

## Histology

Microscopic examination of papillary fibroelastomas demonstrates an acellular myxomatous stroma surrounding an eosinophilic paucicellular core with a flat and cuboidal endothelial lining (Fig. 48-6A and B). They are distinct from myxomas in that they are avascular and do not have the syncytia of spindle-shaped myxoma cells. Immunohistochemical analysis yields the cells comprising the outer lining staining positive for Factor VIII, CD34, and vimentin. The cells in the core of the tumor stain positively for vimentin and S-100, but are negative for CD34 and Factor VIII, two markers for endothelial cells. The stroma demonstrates linear staining of type IV collagen immediately below the endothelial layer that becomes more granular as it gets closer to the core. Also present are linear arrangements of elastin in a similar linear configuration. Among the elastic fibers is the myxoid stroma comprised mainly of an acidic mucopolysaccharide.[20]

## Histogenesis

As with cardiac myxomas, the histogenesis of papillary fibroelastomas is unclear. They have been described as hamartomas, representations of organized thrombi, reactions to endocarditis, or benign neoplasms. Papillary fibroelastomas have been compared with Lambl excrescences, which are also frond-like projections arising from the edges of cardiac valves that are secondary to minor endocardial injuries; these arise from small thrombi and have been shown to be common in autopsy series. In contrast, papillary fibroelastomas are more rare, arise from the middle of the valvular surface, and can arise from areas of endocardium other than the valve edge. Microscopically, organized thrombi do not demonstrate any elastin deposition, and while they do demonstrate areas of proliferating fibroblasts, there is also evidence of capillary formation in the thrombi, which is not present in fibroelastomas.[20] There is some evidence that chronic viral endocarditis may play a role in the development of fibroelastomas, as dendritic cells and remnants of cytomegalovirus have been found within the layers of collagen and elastin in the acellular stroma.[18]

The neoplastic theory of papillary fibroelastomas is supported by what appears to be proliferation by the surface endothelial cells. This is evidenced by the continual production of layers of type IV collagen, which has been demonstrated by immunohistochemical staining. The origin of the neoplastic cells, however, is unknown. The presence of CD34, vimentin, and Factor VIII suggest an endothelial origin, but positive staining for S-100 is inconsistent with an endothelial progenitor. S-100 is a protein of unknown function that is found in malignant melanoma cells as well as chondromatous cells. In the case of cardiac myxomas, the presence of S-100 is thought to support the premise that the myxoma cells are multipotent, with endothelial cells giving rise to papillary fibroelastomas. The data are currently incomplete, and no definite conclusion regarding the origins of papillary fibroelastomas has been established.

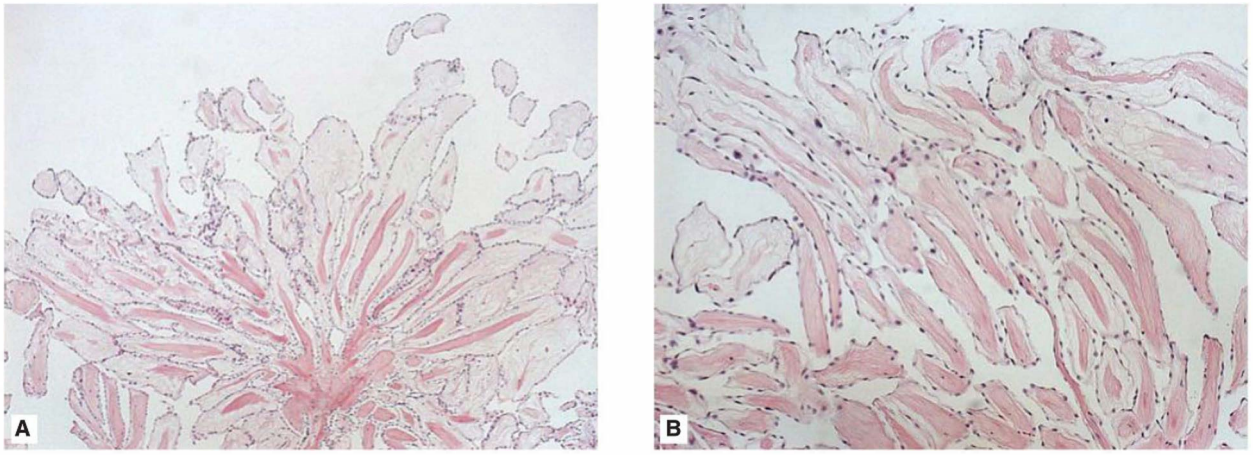



**FIGURE 48-6** Microscopic images of a papillary fibroelastoma. Note the acellular fronds projecting out from the eosinophilic and paucicellular core in **A**. In **B**, a flat endothelial lining surrounds the hyalinized stroma. (Courtesy of Dr. Jonathan Baker, Department of Pathology, University of Texas Southwestern Medical Center.)

## Treatment

Treatment of fibroelastomas is complete surgical excision. The surgical approach is similar to that of myxomas and all chambers and valves should be explored for synchronous lesions. Valve repair or replacement may be necessary depending on how much of the valve is resected. For patients who are not operative candidates, oral anticoagulation has been suggested if feasible in an effort to decrease the risk of systemic embolization from thrombus accumulating on the surface of the tumor. Although oral anticoagulation makes intuitive sense, there are no guidelines to recommend the widespread use of warfarin in this patient population.[19]

## Outcome

The long-term prognosis after complete resection of papillary fibroelastomas is favorable. Life expectancy approaches that of the general population, and the recurrence rate has been shown to be low to nonexistent.[17,19]

## Rhabdomyoma

Rhabdomyomas are most commonly found in children, making up the most common primary cardiac tumor in the pediatric population. They are found in roughly 10 percent of the general population and as such constitute one of the more common benign tumors in adults as well.[3] Most rhabdomyomas arise in the ventricular walls; rarely, they may originate from the atria. Symptoms are usually due to either mass effect resulting in obstruction of blood flow or cardiac conduction abnormalities. Common electrocardiographic changes include bundle branch block, preexcitation, and atrioventricular blocks.[9]

Cases of rhabdomyoma represent a cardiac manifestation of tuberous sclerosis in up to 50 percent of cases.[9] Tuberous sclerosis is an autosomal dominant disease that involves the loss of function of two tumor suppressor genes, TSC-1 hamartin and TSC-2 tuberin. TSC-1 is found on chromosome 9q34 and TSC-2 is found on chromosome 16p13.3. Other manifestations of tuberous sclerosis are brain hamartomas, hyperpigmented skin lesions, pancreatic lesions, and retinal lesions.

Cardiac rhabdomyomas are not capable of mitotic division. The natural history of rhabdomyomas is usually spontaneous regression. For this reason, current therapy involves watchful waiting with surgical intervention only if obstructive symptoms develop, or if conduction abnormalities prove refractory with medical management.

## Fibromas

Cardiac fibromas are solitary benign lesions that arise most frequently in the ventricles with the left being more commonly involved than the right. They arise from fibroblasts in the myocardium and behave similarly to fibromas found in other parts of the body. Children are most commonly afflicted. The most common presentation is consistent with congestive heart failure, but fibromas can also trigger malignant ventricular arrhythmias with sudden death or syncope. Angina pectoris can be due to displacement or occlusion of the coronary arteries by the tumor. Electrocardiography often reveals signs of ventricular hypertrophy, and plain chest radiography can show cardiomegaly with an abnormal contour of the heart and calcifications within the tumor. Calcifications noted on plain film or CT scan are highly suggestive of fibroma versus other cardiac neoplasms.[21] Diagnosis is made with echocardiography.

Gross inspection of the tumor reveals a firm, white mass that usually arises from the ventricle. Histologic evaluation reveals well-circumscribed but not encapsulated tumors located in the myocardium. They are made of fascicles of spindle-shaped cells surrounded by copious amounts of collagen. Cytologic atypia and mitotic figures are usually absent. Areas of calcification are seen in about 56 percent of tumors, which can sometimes be seen on x-ray.[15]

Treatment for cardiac fibromas is surgical excision. Usually, a plane can be developed between the tumor and the myocardium facilitating mass removal. Reconstruction of the ventricular septum is often required and can be accomplished with autologous or bovine pericardium or with a Dacron patch dependent on patient and size factors. One particular challenge occurs when the tumor is located on the superior ventricular septum and passes deep to the left coronary artery or if the mass intimately involves the papillary muscles. In these cases, partial resection of the fibroma has been shown to be effective for alleviating symptoms. In these cases, reoperation has not been necessary, as the residual tumor does not appear to grow to its original size. In addition, partial resection has been shown to eliminate malignant arrhythmias. In cases when the papillary muscles are involved, mitral valve repair or replacement may be indicated. Cardiac transplantation has been suggested for treatment for anatomically complicated fibromas, but given that partial resection may acceptably eliminate the symptoms and risk for sudden death, transplant should only rarely be performed for benign fibromas.[21]

## Lipomas

Cardiac lipomas are benign fatty tissue tumors that make up about 10 percent of benign primary cardiac tumors.[3] They are most often found on the epicardial surface, but they have also been noted to arise in the interatrial septum. Usually, these lesions are found incidentally and do not have any clinical significance. Symptoms, when present, are due to mass effect and obstruction. Microscopically, lipomas are encapsulated and appear as homogenous mature adipocytes with fine septations. Mitoses are rare to nonexistent, and small areas of inflammation can be seen. These areas can be difficult to distinguish from lipoblasts, which would indicate liposarcoma rather than benign lipoma.[22] Differentiation from malignant liposarcoma preoperatively depends upon imaging by CT or MRI to determine if the mass is homogenous, which would suggest a benign lipoma, A heterogenous lesion would be suggestive of a malignancy, which would be an indication for excision. Ulitmately, surgical resection is indicated for symptomatic lesions or when a liposarcoma is suspected. Otherwise, no specific treatment is necessary for cardiac lipomas.

## Lipomatous Hypertrophy

Lipomatous hypertrophy refers to the hyperplasia of naturally occurring fat in the interatrial septum that is continuous with epicardial adipose tissue and, as such, does not constitute true neoplasia. The incidence has been suggested to be as high as 2.2 percent. A higher incidence is associated with obesity and increasing age, with most patients being older than 60 years at the time of presentation. Interestingly, there appears to be an association between female gender and larger lesions. The interatrial septum can become quite thickened to over 3 cm and potentially result in a broad-based mass lesion with atrial filling defects involving the right atrium more commonly than the left. Most cases are asymptomatic and are detected incidentally on transesophageal echocardiography or at autopsy. Presenting symptoms usually include congestive heart failure due to mass effect on the atria, obstruction of the superior vena cava, or intractable supraventricular arrhythmias. There have been some reports of valvular disruption and sudden cardiac death as well.

Grossly, lipomatous hypertrophy appears similar to normal epicardial fatty tissue that spares the fossa ovalis. This creates a bilobed appearance on transverse section of the interatrial septum and on CT scan. It can also appear in the free wall of the right atrium, extend into the root of the aorta, or extend into the atrioventricular groove. Microscopically, the lesions appear to be normal mature adipocytes admixed with brown fat adipocytes marked by multiple vacuoles. Interspersed in the adipocytes are hypertrophied cardiac myocytes with multiple nuclei and cytoplasmic vacuolization. In contrast to lipomas, there is no capsule containing the mass.[22]

Since most lesions are found incidentally, surgery is not usually indicated for lipomatous hypertrophy. Excision is appropriate for patients with congestive heart failure due to atrial compression, atrial arrhythmias refractory to medical management, or valvular dysfunction due to the mass.

## Hemangioma

Hemangiomas are benign tumors that can arise from endothelial cells to form channels of blood. They can be found within the pericardium, myocardium, or endocardium and can originate from any chamber. Hemangiomas comprise approximately 2.8 percent of benign cardiac tumors, and have an equal age distribution and a female preponderance.[23]

Symptoms of hemangiomas can include heart failure due to obstruction, atypical chest pain, arrhythmias with sudden death, pericardial effusion, valvular obstruction, or embolic events. Electrocardiography is usually normal. Diagnosis is made with transthoracic echocardiography and the tumor can be further characterized with transesophageal echocardiography if necessary. On a contrast CT scan, initial imaging shows a filling defect in the affected chamber but follow-up imaging after 5 min shows the tumor enhancing with Hounsfield units equivalent to that of the surrounding blood in the heart. This suggests the highly vascular nature of the tumor and is similar to the CT findings of hepatic hemangiomas. For preoperative planning, an MRI can give additional information with respect to the soft tissue planes around the tumor.[23]

The majority of hemangiomas are about 2 to 3.5 mm in size and can be either polypoid or sessile. Three histological

subtypes of hemangioma exist: cavernous, arteriovenous, and capillary type. The first is marked by many large thin-walled vessels, the second by dysplastic arteries and veins, and the last by smaller vessels similar in appearance to capillaries. These tumors are not encapsulated.[23]

Resection can be technically challenging depending on the location of the tumor and the degree of infiltration into the myocardium. Sometimes, reconstruction of the interatrial septum or even the free wall may need to be performed. Prognosis is good after resection, but long-term postoperative follow-up is warranted to monitor for recurrence.

### Cystic Tumors of the Atrioventricular Nodal Region

These rare lesions, formally referred to as mesotheliomas of the atrioventricular node, represent cystic lesions thought to be epithelial rests of endodermal origin that arise immediately adjacent to the atrioventricular node. The most common presenting symptom is sudden death due to ventricular arrhythmias and, accordingly, most are found on autopsy studies. Interestingly, they have been discovered in patients from infancy to 70 years of age, and older patients presenting with sudden death often do not have a history of syncope or palpitations.[24] Electrocardiography usually reveals various degrees of heart block and QRS narrowing. The lesion can be detected by MRI, CT, or echocardiogram. Treatment involves resection with pacemaker placement. There are only rare reports of antemortem detection and successful surgical treatment in the literature.[25]

### Cardiac Neurilemomas

Cardiac neurilemomas, or schwannomas, are rare benign tumors that are thought to arise from the cardiac branches of the vagus nerve or the cardiac plexus. They normally arise on the right side of the heart near the interatrial septum. Only 14 cases have been reported in the literature, and these cases show a female predominance (10 females and 4 males) with age ranging from 12 to 72 years. They can be on the exterior of the heart and cause compression of the pulmonary veins and superior vena cava. Diagnosis is made histologically with the demonstration of areas of spindle-shaped cells with rare mitoses and strong uniform staining for S-100. Of note, frozen sections sent intraoperatively can be easily misinterpreted, and the final diagnosis must rest on the formal pathological and immunohistochemical studies on the final specimen.[26] Treatment is surgical excision, and the prognosis is excellent with complete resection.

## MALIGNANT TUMORS

One quarter of all primary cardiac neoplasms are malignant.[3] Of these, sarcomas are by far the most common with a very small percentage of primary cardiac lymphomas essentially comprising the rest. Cardiac malignancies generally portend a poor prognosis, and almost all patients eventually succumb to their disease. The median survival from time of diagnosis has been reported to be 6 to 18 months. When technically feasible, surgical resection is the treatment of choice, but unfortunately this is rare as most are diagnosed after the tumor has reached an advanced state. Debulking of these tumors for obstructive symptoms can provide palliation but is controversial. Although chemotherapy plays a dominant role in the treatment of lymphoma, the role of adjuvant chemoradiation in sarcomas has not been clearly defined.[27]

Differentiating benign from malignant disease preoperatively can be difficult but is crucial as earlier surgical intervention provides a better chance for cure. Features that suggest malignancy are rapid growth rate, local invasion on imaging, intracavitary lesions that also involve the chamber wall, and hemorrhagic pericardial effusion. These symptoms, however, are nonspecific and can be seen with benign lesions as well.

### Sarcomas

Sarcomas comprise the vast majority of primary cardiac malignancies and are the second most common type of primary cardiac tumor after myxomas. Believed to arise from pluripotent mesenchymal cells, several histologic subtypes of sarcomas exist with angiosarcoma being the most common. Other notable histologies include rhabdomyosarcoma, liposarcoma, myxosarcoma, leiomyosarcoma, malignant fibrous histiocytoma, and synovial cell sarcoma, but many are undifferentiated and are not otherwise classifiable. Most sarcomas arise on the left side of the heart, with the exception of angiosarcomas, which tend to arise on the right side.[2,27] Notably, surgical resection is related more to the size and location of the tumor and the associated involved structures rather than the histological subtype of the tumor.

Clinically, the most common presenting symptom is dyspnea on exertion due to an obstructing tumor. Like other cardiac tumors, sarcomas can present with symptoms due to embolic events, chest pain, rhythm disturbances, or constitutional symptoms. In addition, they may present with evidence of metastasis to bones or to skin.[2]

### Epidemiology

Primary cardiac sarcomas have an incidence between 16 and 35 percent of all cardiac tumors with an equal gender distribution. The median age at presentation is 41 years, and the disease is most commonly diagnosed in young- to middle-aged adults with children and infants being affected only rarely.

### Pathology

All sarcomas arise from mesenchymal cells but are classified based upon the differing patterns of differentiation.

Undifferentiated sarcomas do not have enough characteristic histological features to place them in a specific subtype.

Angiosarcomas have endothelial differentiation. They are similar to benign hemangiomas in appearance, but they demonstrate more atypia in the cells lining the vascular lumens and more mitotic figures. The tumor can also create capillary channels that do not have any discernible lumen. In less differentiated angiosarcomas, the endothelial origin of the cells is not as evident, and the cells do not form well-defined vascular structures. In these cases, the pathologic diagnosis can be inferred by lakes of blood within the tumor. Although not sensitive, it should be noted that angiosarcoma cells will stain positive for factor VIII due to their endothelial origin.[2]

Cardiac malignant fibrous histiocytomas appear similar to those found in other parts of the body. Two tumor cell types predominate: spindle-shaped fibroblastic cells with intracytoplasmic filaments and enlarged endoplasmic reticulum and the more pleomorphic histiocytoid cells marked by scattered lysosomes and lipid inclusions. Malignant fibrous histiocytoma can appear with a myxoid background and can also have areas that are paucicellular or acellular that can appear similar to myxomas, leading to a pathologic misdiagnosis. In general, however, malignant fibrous histiocytomas are more cellular and show a higher degree of atypia. In addition, the vascularity differs in the two types of tumor: in myxomas, the vessels are small, thin-walled capillaries, whereas in malignant fibrous histiocytomas, the vessels are thicker walled and have more prominent, branching vessels.[2]

Fibrosarcomas histologically appear similar to fibroblasts. They are polypoid tumors that can be intracavitary and invade the myocardium. The cells appear spindle-shaped, similar to malignant fibrous histiocytoma; the pleomorphic histiocytoid cells are not present. The cells are visible in a background of collagen or myxoid matrix.

Rhabdomyosarcomas are a rare type of sarcoma and can be found in any chamber of the heart with equal incidences. They can become quite large, up to 10 cm. On microscopic examination, rhabdomyosarcomas can appear similar to striated muscle. The typical myocyte structure of thick and thin filaments can be variably preserved with visible Z-bands, abundant glycogen, and many mitochondria. The presence of rhabdomyoblasts will confirm the diagnosis.[2]

## Surgical Treatment

As with the majority of cardiac tumors, complete surgical excision is the only proven therapy for primary cardiac sarcomas. When technically feasible, complete resection of the tumor can result in a median survival of almost 24 months.[28] The surgical techniques are similar to those for benign tumors. Patients are placed on cardiopulmonary bypass with superior and inferior vena cava cannulation and aortic return when possible. Larger lesions require more radical resection, which can result in the complete excision of atria, roots of the aorta or pulmonary artery, pericardium, or sections of either ventricle. Reconstruction of these structures can be done with bovine or autologous pericardium or synthetic materials such as Dacron. One institution found that either atrium could be replaced in its entirety, and up to 30 percent of the right ventricle could be patched while still maintaining adequate cardiac function. A major sign of unresectability is involvement of the fibrous cardiac skeleton. Coronary bypass may be necessary if ligation of a coronary artery is required due to tumor involvement. One aggressive surgical technique that has been utilized is cardiac autotransplation, whereby the heart is explanted from the mediastinum and the operation is performed on the back table before the heart is reimplanted into the chest. In addition to resecting the cardiac tumor, metastasis to the lungs can be surgically treated with lung parenchymal sparing resections. Adding these procedures, however, may increase operative mortality.[28]

In the absence of metastatic disease, cardiac transplantation has been used as a potential therapy for locally unresectable cardiac tumors. Cardiac transplantation has been shown to significantly add to survival and it has been suggested that postoperative chemotherapy may be of benefit. One strategy that has been employed is the identification of a proper donor allograft and a backup recipient. The patient is then taken to the operating room and resection of the cancer is attempted prior to allograft recovery. If resection is determined to not be feasible then a standard cardiac transplantation is performed. If resection is deemed to be possible then the donor allograft can be implanted into the backup recipient.[29] Although controversial, palliative debulking of sarcomas has been reported for cases of intracardiac mechanical obstruction or obstruction of the pulmonary artery.

## Medical Therapy

Both chemotherapy and radiation therapy have been employed in the treatment of cardiac sarcomas, but their role in treatment is still unclear. Adjuvant chemotherapy with paclitaxel, doxorubicin, ifosfamide, gemcitabine, or taxoterene is commonly used. Due to the low overall incidence of the disease, no studies exist that can definitively support the use of chemotherapy; chemotherapy should be considered on a case-by-case basis. Despite this inherent weakness in the literature, the existing data has suggested that chemotherapy with multiple agents may enhance the survival advantage achieved with surgery. Furthermore, radiation therapy administered postoperatively may increase survival as well. Neoadjuvant chemotherapy has also been suggested to decrease the size of the tumor to make the resection more technically feasible, but there are no data currently to make such a recommendation. For patients in whom surgery is not possible due to the extent of disease, significant comorbidities, or prohibitive tumor anatomy, treatment is purely palliative.

## Outcomes

The prognosis of primary cardiac sarcoma is dismal. Without surgery, median survival has been reported to be 10 months.

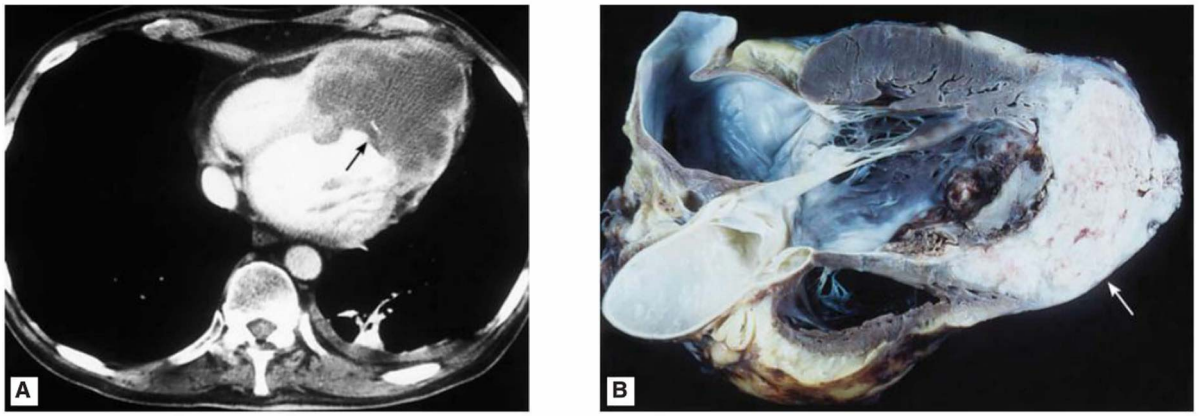



**FIGURE 48-7** CT scan demonstrates a large left ventricular lymphoma (marked by arrow) involving the cardiac wall in **A**; **B** demonstrates an autopsy specimen of a left ventricular lymphoma. (Reprinted from Araoz PA, Eklund HE, Welch, TJ et al. CT and MR imaging of primary cardiac malignancies. *Radiographics* 1999;19:1421–1434. With permission from the Radiological Society of North America.)

If complete resection is performed, the median survival is improves to 23.5 months.[28] Cardiac transplantation has been shown to improve survival, but more data are needed to fully analyze the effects of multimodality therapy.

## Lymphoma

Primary lymphoma of the heart, defined as the presence of cardiac lymphoma without any evidence of extracardiac disease, is extremely rare. It constitutes only 1.3 percent of primary cardiac tumors and less than 0.5 percent of all extranodal lymphomas. In contrast, lymphoma with secondary cardiac involvement, defined as cardiac lymphoma in the setting of nodal or other organ involvement, is common, with up to 20 percent of non-Hodgkin lymphoma patients having cardiac involvement at autopsy. B-cell differentiation is the most common (accounting for up to 80 percent cases of primary cardiac lymphoma in immunocompetent patients), but there have been reports of cardiac T-cell lymphoma as well. The mean age at presentation is 60 years. The tumors arise most commonly in the right atrium with the right ventricle being the second most common location. However, it should be noted that, in up to 75 percent of cases, multiple cardiac chambers are involved.[30]

Clinical presentation can be varied with most patients presenting with symptoms of right-sided heart failure. Other presenting symptoms can include pleuritic pain, syncope, an embolic event (usually pulmonary, given the predilection for right-sided tumors), pericardial effusion or tamponade, and pleural effusion. Constitutional B symptoms can also be present, but are relatively uncommon. Serum studies may show an increase in lactate dehydrogenase and erythrocyte sedimentation rate. Electrocardiography may demonstrate nonspecific findings, such as atrioventricular block.

As with other cardiac tumors, cardiac lymphomas can usually be evaluated with transthoracic echocardiography, reserving transesophageal echocardiography for better characterization and description. Cardiac CT can aid in defining pericardial involvement and extracardiac foci of disease (Fig. 48-7A and B). MRI, however, is considered the best modality for diagnosing cardiac lymphomas as well as monitoring tumor response to chemotherapy. On T1-weighted imaging, the tumor will appear as poorly delineated, slightly hypointense, heterogenous lesions. T2-weighted imaging renders the tumor isointense to the surrounding myocardium. Diagnosis can also be made by studying the cytology of drained pericardial or pleural effusions. Atypical lymphoid cells can be present in the fluid, and the diagnosis of lymphoma can be made with immunohistochemical staining. In patients in whom cardiac lymphoma is suspected, but there is no accompanying effusion to analyze, biopsy via exploratory thoracotomy can make the diagnosis.[30] Unlike other tumors of the heart, a firm diagnosis of lymphoma is necessary because treatment will not be surgical.

## Treatment

In contrast to other cardiac tumors, surgical excision is not the first-line treatment for cardiac lymphoma. Chemotherapy with anthracycline and anti-CD-20-based treatment are the mainstays of therapy,[9] and radiation therapy has been shown to increase survival. Surgical debulking has been used for relief of obstructive symptoms for palliation, but resection is not recommended as a primary treatment modality. Cardiac transplantation has been reported and is associated with some success.[30]

## Outcome

Due to the often late diagnosis, primary cardiac lymphoma generally carries a poor prognosis. Without therapy, survival is around 1 month. With an effective chemoradiation regimen, survival can be as long as 5 years.[30]

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## PRIMARY CARDIAC TUMORS BOARD REVIEW QUESTIONS (CHAPTER 48)

1. The primary treatment of which of the following tumors does not involve surgical excision?
   A. Myxoma
   B. Papillary fibroelastoma
   C. Rhabdomyoma
   D. Liposarcoma
   E. Rhabdomyosarcoma

2. A 10-year-old boy presents to the ER after a syncopal episode. He denies any chest pain, but his mother reports that he is not able to run as much as other children because he has trouble catching his breath. EKG does not show any abnormalities, but the chest x-ray shows an enlarged left ventricle with calcifications in the same region. Echocardiogram demonstrates a left ventricular mass that seems to involve the papillary muscles. What is the best management of this mass?
   A. Medical therapy with β-blockers and/or calcium channel blockers
   B. Attempt a complete resection of the mass with autotransplantation
   C. Cardiac transplantation
   D. Partial resection of the mass
   E. Medical therapy with oral anticoagulation

3. A 42-year-old female presents to the clinic with complaints of worsening dyspnea on exertion. EKG and chest x-ray are normal. Transthoracic echocardiogram demonstrates a left atrial pedunculated mass with a short visible stalk arising from the interatrial septum. What is the most appropriate management of this tumor?
   A. Proceed to surgery for excision of the tumor.
   B. Obtain EKG-gated CT scan to further evaluate the anatomy of the tumor.
   C. Obtain cardiac MRI to determine if there is any involvement of the interatrial septum and right atrium.
   D. Provide medical therapy with a β-blocker and oral anticoagulation with repeat echocardiogram in 6 months.
   E. Obtain an angiogram of the left atrium and ventricle to determine the size of the mass and its relation to the fossa ovalis.

4. Which of the following therapies for cardiac sarcoma is associated with the longest survival?
   A. Chemotherapy with Doxorubicin, Paclitaxel, and Gemcitabine
   B. Radiation therapy alone
   C. Radiation therapy with chemotherapy
   D. Resection using the autotransplantation technique
   E. Surgical debulking of the tumor to relieve associated mitral valve orifice obstruction

5. Which of the following characteristics would render a primary sarcoma of the heart unresectable?
   A. Involvement of the mitral valve annulus
   B. Involvement of two-thirds of the left atrial wall
   C. Involvement of two-thirds of the right atrial wall
   D. Involvement of the right ventricular free wall
   E. Involvement of the aortic valve

## ANSWERS

1. **Answer: C.** Surgical excision is the mainstay of management of most benign cardiac tumors as well as sarcomas when feasible. Rhabdomyomas, however, are unable to proliferate, and as such, will usually spontaneously regress. Resection is only indicated in cases of severe obstruction and failure to regress. Rhabdomyosarcoma, like other sarcomas, is best treated surgically if detected at an early stage.
2. **Answer: D.** This case likely represents a ventricular fibroma. These tumors are common in children and present with symptoms of heart failure and arrhythmias. Calcifications noted on chest x-ray are highly suggestive of fibroma. While complete excision is the best therapy, partial excision has been shown to reduce symptoms as well when the mass is anatomically difficult to resect. Medical therapy is unlikely to be helpful in this patient. A radical solution, such as autotransplantation, is not necessary in this case as partial resection will suffice. Cardiac transplantation has been described as an option for ventricular fibroma, but should only be used as a last resort when there are no other surgical options.
3. **Answer: A.** The presence of a stalk arising from the interatrial septum is highly suggestive of an atrial myxoma. With this information from an echocardiogram, no more workup is necessary for the mass. The only other study to be considered would be a coronary angiogram to determine the need for a simultaneous coronary artery bypass graft. Given the propensity for embolization, myxomas should be resected expediently.
4. **Answer: D.** Cardiac malignancies have a very poor prognosis. The only proven therapy to significantly prolong survival is resection. Chemotherapy and radiation therapy have been shown to potentially prolong survival when combined with surgery, but they have not been shown to prolong survival alone. Surgical debulking is a palliative procedure that is not intended to increase survival.
5. **Answer: A.** Any of these scenarios would make resection of the mass difficult. The single-most important factor is the involvement of the fibrous skeleton of the heart. Either atrium can be replaced with pericardium (autologous or bovine) or Dacron, as can up to 30 percent of the right ventricle. The aortic root can also be replaced if necessary. Involvement of the mitral valve annulus would likely involve the fibrous skeleton of the heart and therefore would not be resectable.

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49

# The Immunobiology of Thoracic Transplantation[1]

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**KEY CONCEPTS**

- The major histocompatibility complex (MHC) consists of a genomic region that encodes a large and diverse group of proteins that are expressed on all cells. The two major classes of MHC molecules include class I molecules that are found on all nucleated cells and present antigen to CD8 positive ($CD8^+$) "cytotoxic" T cells and natural killer (NK) cells. Class II MHC molecules occur on antigen presenting cells and present antigen to CD4 positive ($CD4^+$) "helper" T cells.
- Normal development of immunotolerance occurs primarily in the thymus whereby T cells displaying different T-cell receptor complexes interact with thymic epithelial cells.
- Antigen presenting cells (APCs) are the most potent initiators of alloimmune responses because they express high levels of both MHC class I and class II antigens. APCs also express costimulatory molecules that provide secondary signals necessary for expansion of the T-cell response to alloantigens.
- T-cell receptor activation by MHC activates calcineurin. Calcineurin, in turn, activates a transcription factor that increases the interleukin-2 (IL-2) production and other cytokines.
- Secreted IL-2 binds to immune cell surface IL-2 receptors (IL-2R) and stimulates expansion of the local immune cell population (predominately T cells), resulting in increased inflammatory cells in the donor organ and injury manifested as epithelial cell or myocyte death.
- B cells mediate the antibody response to alloantigen, specifically donor endothelial cells. Antibody binding to alloantigen activates a complement cascade that causes endothelial injury resulting in interstitial hemorrhage, microthrombosis, and an influx of inflammatory cells.
- Hyperacute rejection occurs within the first 24 h after transplantation and is generally dependent on the presence of preexisting anti-human leukocyte antigen (anti-HLA) antibodies that coat the endothelium and activate complement.
- One known mechanistic pathway of bronchiolitis obliterans syndrome, or chronic lung allograft rejection, is the sensitization of $CD4^+$ T cells to MHC class I and class II molecules. Much of the resultant lung injury is from indirect pathway activation.
- Chronic allograft vasculopathy observed in cardiac allografts is thought to result from injury to the coronary artery endothelium. Sources of injury include immunologic (e.g., innate, T-cell–mediated, antibody-mediated) and nonimmunologic (e.g., diabetes, obesity, hyperlipidemia, hyperhomocysteinemia, and CMV) factors.
- During the first year after transplantation, acute rejection is noted in about 25 percent of heart transplant recipients and 36 percent of lung transplant recipients.

## OVERVIEW OF CHAPTER

After the technical challenge of lung or heart transplantation has been successfully achieved, the process of maintaining a healthy graft begins. For this, a general understanding of the immunobiology of thoracic transplantation is needed. This chapter will provide a background on the immune system and allorecognition. It will describe how the immune system mediates rejection of lung and heart transplants, types of organ rejection, and the histologic appearance of rejection. It

[1]The authors would like to acknowledge Norman Barker and Dr. Peter Illei for their help with the images in this chapter.

will further describe methods to monitor allograft rejection and the criteria upon which rejection is characterized. Finally, the chapter will cover basics of immunomodulation therapy.

## History of Primary Graft Failure and an Understanding of the Role of Allorecognition

Experimental heart transplantation developed slowly through the 1940s and 1950s, but became established in the laboratory of Dr. Norman Shumway by the mid-1960s. Human heart transplantation was first performed by Dr. Christian Bernard in 1967. Heart transplant outcomes were initially poor due to quick rejection of the organ. Experimental lung transplantation in mammals occurred throughout the first half of the 20th century. The first human lung transplantation occurred in 1963, although "successful" transplantation did not occur until the early 1980s. For both organs, early survivability was dependent on a number of factors, but key among them was an understanding and control of organ rejection. These early transplants failed because there was no effective way to control organ rejection without overly suppressing the immune system leading to fatal infections. The revolution in solid organ transplant was made possible by the immunosuppressive drug cyclosporine, discovered in the mid 1970s and introduced clinically in 1983. It prevented acute rejection of the organ, but allowed the body to ward off infectious agents. Thus successful organ transplantation is dependent upon a keen understanding of the interaction of the immune system with the transplanted organ. Our understanding of this interaction is focused on the role of the major histocompatibility complex (MHC) and the innate immune system in solid organ rejection.

## MAJOR HISTOCOMPATIBILITY COMPLEX

The MHC is one of the essential parts of the immunoregulatory process. The MHC genomic region encodes a large and diverse group of proteins that are expressed on all cells. These MHC proteins present antigen (polypeptide fragments of cell proteins) to immune cells, predominantly T cells. There are two major classes of MHC molecules. Class I molecules are found on all nucleated cells and present antigen to CD8 positive ($CD8^+$) "cytotoxic" T cells and natural killer (NK) cells. Class II MHC proteins occur on antigen presenting cells (APCs) and present antigen to CD4 positive ($CD4^+$) "helper" T cells. In the lung and heart, native dendritic cells are the primary MHC class II positive APCs.

## RECOGNIZING SELF AND DEVELOPING TOLERANCE

With all human cells constantly presenting antigen to T cells, one might wonder why our bodies are not under constant immunologic attack. The answer is that through our first year of life, our body learns to differentiate between self and nonself antigens. This process occurs primarily in the thymus in which an enormous diversity of T cells each displaying a different T-cell receptor complex interacts with thymic epithelial cells. Only those T cells that have an intermediate affinity for self-antigen MHC complexes (an ability to recognize, but not react) are allowed to survive. T cells with either no affinity or high affinity to self peptide MHC complexes are removed. Thus, after the first year of life, our T cells have developed the capability to perform immunosurveillance and differentiate between self and nonself antigens presented by MHC complexes.[1]

## ALLORECOGNITION PATHWAYS

APCs are the most potent initiators of alloimmune responses because they express high concentrations of both MHC class I and II antigens (Fig. 49-1). The MHC class II antigens are required to activate CD4 helper T cells. APCs also express numerous costimulatory molecules that provide secondary signals necessary for expansion of the T cells' response to the target antigens. APCs can participate in three pathways of allorecognition. All three pathways are involved in lung and heart rejection. The direct pathway is the mechanism by which recipient T cells recognize nonself antigen present on donor APCs. Transplants contain large numbers of donor APCs at the time of transplantation that are progressively replaced by recipient APCs. The indirect pathway occurs when necrotic or apoptotic cellular debris from donor cells are taken up by recipient APCs. These nonself antigens are then displayed via MHC class II molecules resulting in a $CD4^+$ cell-driven process. A third potential pathway is the semidirect pathway. Here, small cellular vesicles (exosomes) containing MHC move from a donor APC to a recipient APC and stimulate both $CD4^+$ and $CD8^+$ T cells.[2] In addition to the described T cell MHC interaction, a costimulatory event must occur to optimally activate the T-cell response. The best studied costimulation interaction is between the CD28 protein on the T cell and a B7 molecule (B7-1 and B7-2; CD 80 and 86, respectively) on the APC.[3] A new immunosuppressive agent, LEA29Y (belatacept), blocks this interaction, although it is not yet used in thoracic transplantation.

## Secondary Stimulation of T-cell Response

Once a T cell has become activated, a number of inflammatory pathways become upregulated. The pathways described here are all targeted by immunosuppressive drugs that will be covered later in this chapter. T-cell receptor activation by MHC activates calcineurin. Calcineurin, in turn, activates a transcription factor (NF-AT) which increases the production of interleukin-2 (IL-2) and additional cytokines (Fig. 49-1). Secreted IL-2 binds an IL-2 receptor (IL-2R) on the cell surface stimulating expansion of the local immune cell population (predominantly T cells). This cell proliferation is partly

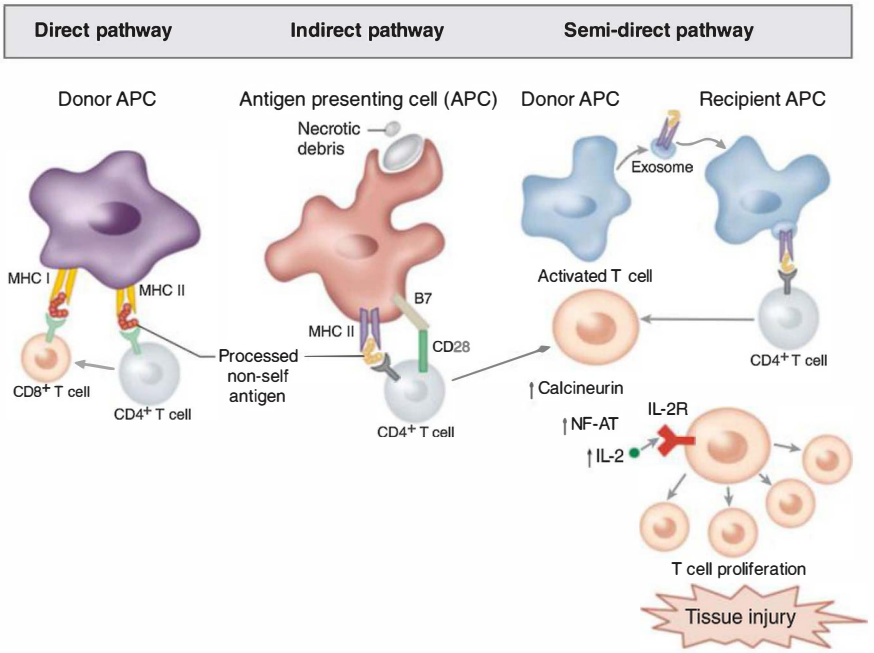



**FIGURE 49-1** Mechanisms of cellular rejection. In the direct pathway, all cells can express nonself antigens to T cells by MHC I molecules. In the indirect pathway, antigen presenting cells (APCs) (usually dendritic cells) phagocytize necrotic debris and present this to $CD4^+$ T cells via MHC II molecules. In the semidirect pathway, donor APCs release exosomes with MHC II molecules that are taken up by recipient APCs. These recipient APCs present nonself antigen to $CD4^+$ T cells. Stimulation of T cells by nonself antigen cause an increase in calcineurin, which increases the nuclear transcription factor NF-AT, which results in elevated IL-2. IL-2 acts in autocrine and paracrine fashion to stimulate local T-cell proliferation that causes tissue injury.

mediated by a direct stimulatory effect of IL-2R on mTOR which regulates the cell cycle.[3] The result of this activation pathway is increased inflammatory cells in the donor organ and injury seen as epithelial cell or myocyte death.

## INNATE IMMUNE SYSTEM

In distinction to the adaptive immune response that is defined by antigen specific receptors on lymphocytes (T cells and B cells), the innate immune system encompasses mediators and cells with invariant receptors (Table 49-1). These include proteins of the complement system as well as an array of cells, notably platelets, granulocytes, monocytes, and macrophages. Components of the innate immune system evolved to survive pathogens and tissue injury (Fig. 49-2). Toll-like receptors (TLR) and mannose binding lectin (MBL) are good examples of what Janeway[4] termed pattern recognition receptors that bind to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). PAMPs include structural motifs unique to prokaryotes, such as lipopolysaccharide (LPS), bacterial lipopeptides, flagellin, and unmethylated DNA. DAMPs are intracellular or cryptic molecules that are exposed by tissue disruption or produced by cells in response to stress. Among the best-defined DAMPs are heat shock proteins (HSP) and fragmented hyaluronan. Other DAMPs such as high-mobility group box 1 (HMGB1) and IL-33 are located in the nucleus of live cells and released by necrotic cells.

Toll receptors were discovered in fruit flies because genetically deficient flies had morphogenic defects and were susceptible to fungal infections. On the basis of sequence homologies more than 10 TLRs have been identified in mammals. In humans, TLR 1, 2, and 6 can form heterodimers and TLR4 forms homodimers on the surface of leukocytes and parenchymal cells where they bind signature PAMPs and DAMPs (Fig. 49-3). TLR4, for example, binds LPS and fragmented hyaluronan.[5] Other TLRs, such as TLR3, are located on intracellular endosomes and recognize viral and bacterial RNA or DNA. Cell surface TLRs signal through MyD88 to upregulate a group of proinflammatory cytokines, including TNFα, IL-1, IL-6, and IL-12 as well as the chemokines IL-8 and MCP-1 that attract neutrophils and monocytes. TLR4 also signals through TRIF as does the intracellular TLR3 to upregulate IFNα and β (Fig. 49-3).

MBL is integrated into the complement system of mammals as one of three initiators of the complement cascade. MBL is a member of the collectin family of proteins that are characterized by collagen-like tails with globular lectin heads, hence "col-lectin."[6] The lectin heads can bind to carbohydrates terminating in mannose, fucrose and N-acetylglucosamine (GlcNac) that typify bacteria. The

**TABLE 49-1: Examples of Pattern Recognition Receptors of the Innate Immune System that are Relevant to Transplantation**

| Pattern Recognition Receptor (PRR) | Location | Pathogen | Apoptotic/Necrotic or Stressed Cells |
|---|---|---|---|
| C reactive protein | Fluids[a] | Bacteria/fungi | Yes |
| Properdin | Fluids[a] | Bacteria/fungi | Yes |
| Mannose binding lectin (MBL) | Fluids[a] | Bacteria/fungi | Yes |
| Ficolins (L and H) | Fluids[a] | Bacteria/fungi | Yes |
| Surfactants (A and D) | Fluids[a] | Bacteria/fungi | Yes |
| C1q | Fluids[a] | Bacteria/fungi | Yes |
| TLR1, 2, 4, 5, 6 | Cell membrane | Bacteria/fungi | Yes |
| Dectin-1 | Cell membrane | Fungi | Yes |
| TLR3, 7, 8, 9 | Intracellular[b] | Viruses/bacteria | |
| NOD-like receptors | Intracellular[b] | Bacteria | |

[a]Plasma, interstitial fluids, etc.

[b]Membranes of intracellular compartments, for example, endosomes and lysosomes.

affinity of these reactions is low, but MBL forms oligomers of two, three, four, or six molecules that bind arrays of repeated carbohydrate motifs with relatively high avidity. Homologues of collectins and MBL have been identified in invertebrate animals such as sea squirts. These animals lack most of the remainder of complement components. Therefore, collectins arose as primitive pattern recognition molecules that opsonized bacteria for phagocytes. They also opsonize subcellular debris from injured or senescent cells for removal by phagocytes. In mammals, innate immunity functions both independently and in conjunction with the adaptive immune response.[7]

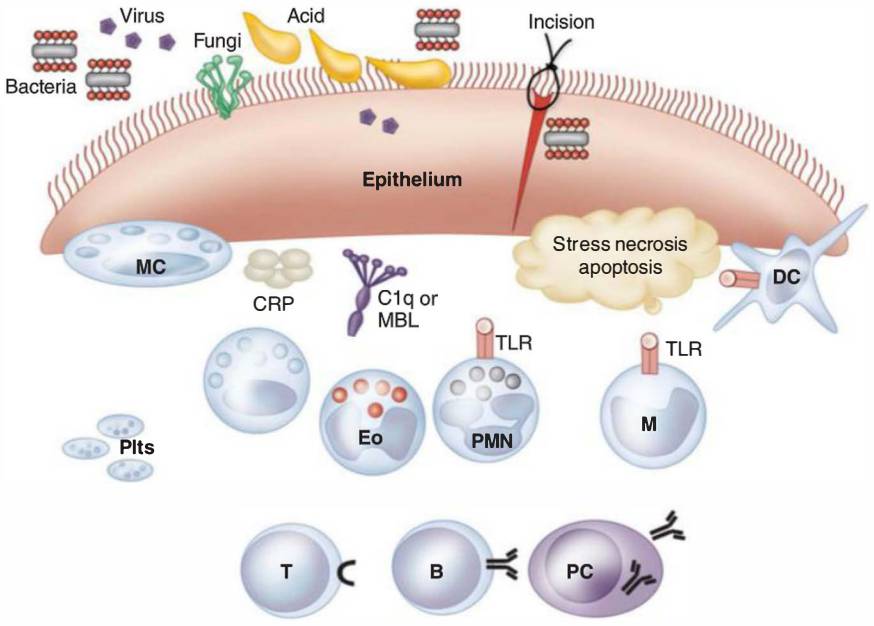



**FIGURE 49-2** Overview of the elements of the innate immune system. Most pathogens (fungi, bacteria, and viruses) are prevented from entrance to the body by chemical and physical barriers of skin and mucosal surfaces. The mucosal surface of the lung has the additional protection of cilia that move mucus along the surface. These barriers can be breached by toxic materials (e.g., gastric juices refluxed into the lung) or surgical incisions. These same insults can cause cells to undergo stress, apoptosis, or necrosis. Pathogens and damaged cells are recognized by soluble or cell-bound receptors of the innate immune system. These include C-reactive protein (CRP), complement components (C1q and MBL), and Toll-like receptors (TLR). Cells of the innate immune system, such as neutrophils (PMN), macrophages (M) and dendritic cells (DC), mast cells (MC), eosinophils (Eo), and platelets (plts), can react through TLRs and receptors for complement or cytokines. Innate immunity provides the immediate response that allows the cells of the adaptive immune system (T cells, B cells, and plasma cells) time to respond.

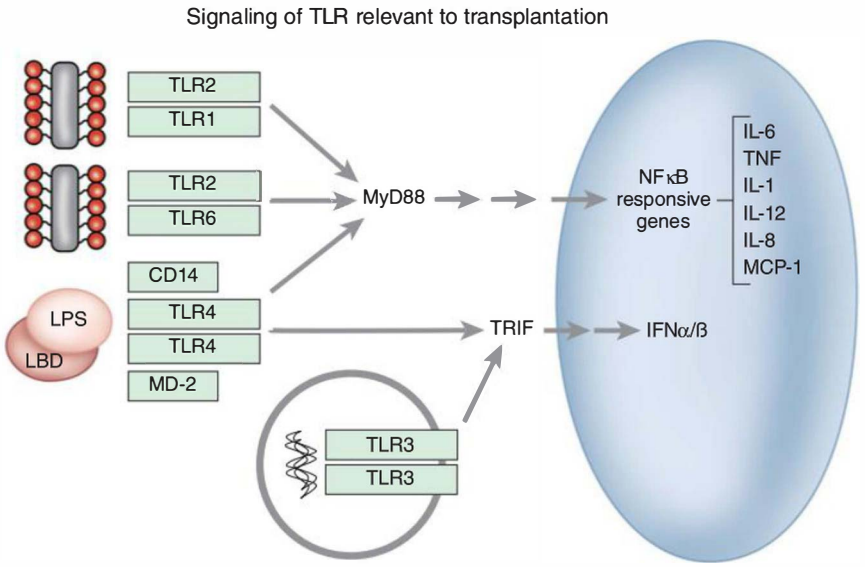



**FIGURE 49-3** Cytokine responses signaled by Toll-like receptors (TLR). TLR on the external cell membrane recognize cell wall components of bacteria and fungi. TLR in endosomal membranes recognize RNA or DNA from viruses and bacteria. Signaling pathways through MyD88 cause the upregulation of a group of nuclear factor kappa B responsive genes including those for the proinflammatory cytokines IL-6, TNFa, IL-1, IL-12, IL-8 and MCP-1). Signaling through the TRIF pathway causes upregulation of type I interferons (IFN).

## INNATE IMMUNE SYSTEM IN PERIOPERATIVE GRAFT INJURY

Unlike adaptive immune responses, which require days to generate, the invariant receptors of the innate immune system provide immediate responses in the postoperative period. Of particular relevance to transplantation are the innate immune responses to ischemia imposed by organ procurement followed by reperfusion when the transplant operation is completed (Table 49-2). Unmitigated ischemia–reperfusion injury is characterized by activation of the complement cascade, platelets, and granulocytes. The ensuing tissue injury results in macrophage infiltration. Even with current preservation solutions, which are designed to diminish this injury, early protocol biopsies often contain some evidence of ischemic injury histologically identifiable by macrophage infiltrates and deposits of complement split products (C4d and C3d) on damaged myocytes.

Organs from deceased donors are subject to multiple insults that can augment innate immune responses. These include sequella of traumatic injury, brain death, and various emergency interventions (Fig. 49-2). Surgical procedures cause tissue injury resulting in exposure of DAMPs and initiation of wound healing responses. In addition, incisions break mechanical and chemical barriers, providing portals for infectious agents and stimulation of innate immunity through PAMPs.

Thoracic organ transplants that require cardiopulmonary bypass have additional inciting stimuli for the innate immune system. These include the bioincompatible surfaces of the bypass equipment that cause complement activation. Any platelet transfusions also introduce partially activated platelets that release chemokines and cytokines. The inflammatory effects of the innate immune responses can be decreased by administration of steroids postoperatively.

## INTERACTIONS OF THE INNATE IMMUNE SYSTEM WITH ADAPTIVE IMMUNITY

Components of the innate immune system facilitate de novo adaptive immune responses and augment preexisting or ongoing adaptive immune responses. Macrophages in ischemic sites, for example, can upregulate MHC class II expression and present antigen to T cells. Preexisting or newly induced antibodies can activate complement and generate biologically active split products that chemoattract and activate neutrophils and macrophages. As a result, these are the most common leukocytes in antibody-mediated rejection (AMR). C5 is a pivotal component of complement because it is cleaved into two key split products when it is activated: C5a, which is a powerful chemoattractant and activator of neutrophils and macrophages; and C5b that initiates the formation of the membrane attack complex (C5b–C9) that can lyse endothelial cells. This has led to the development of therapeutic agents to block C5 including monoclonal antibodies to C5, small-molecule antagonists for C5a, and soluble receptors for C5a.

**TABLE 49-2: Stimulants to the Innate Immune System that are Relevant to Transplantation**

| Event | Donor | Recipient | Innate Responders |
|---|---|---|---|
| | | **Pretransplant** | |
| Fatality | Major trauma | | Platelet activation, etc. |
| Organ procurement | Organ ischemia | | Complement, neutrophils, platelets, macrophages |
| Pretransplant maintenance | | Dialysis, ventricular assist device | Complement, neutrophils, platelets, macrophages |
| Intraoperative procedures | | Surgery, cardiopulmonary bypass | Complement, neutrophils, platelets, macrophages |
| | | **Posttransplant** | |
| Postoperative | | Organ reperfusion | Complement, neutrophils, platelets, macrophages |
| | | Antibody-mediated rejection | Complement, neutrophils, platelets, macrophages |
| | | Cell-mediated rejection | Macrophages, platelets |
| | | Infectious complications to the lung | Complement, neutrophils, macrophages |

Cells of both the innate and adaptive immune systems express receptors for complement split products. Macrophages express receptors for C5a that stimulate the upregulation of receptors for other complement split products and for the $F_c$ of antibodies. Therefore, interactions of macrophages with C5a increase their responses to antibodies and complement. T cells also have receptors for C5a, and B cells have receptors for C3d, which increase their responses triggered by their antigen-specific receptors.

## ANTIBODY-MEDIATED IMMUNE RESPONSE

In addition to innate and T-cell–mediated immune responses, B cells also remain vigilant against transplanted tissues. Here, B cells make antibodies that target donor endothelium. These antibodies activate the complement cascade of innate immunity. As a result the long-lived split products of complements C3 and C4 (C3d and C4d) covalently bind to the endothelium. This AMR can occur immediately after transplantation or weeks to months to years later. Hyperacute rejection occurs within the first 24 h after transplantation and is generally dependent upon the presence of preexisting anti-human leukocyte antigen (anti-HLA) antibodies that coat the endothelium and activate complement. Complement then causes endothelial injury resulting in interstitial hemorrhage, microthrombosis, and often an influx of inflammatory cells. As a result of cross-matching for antibodies to HLA (see Chapter 11), hyperacute rejection rarely happens in heart and lung transplantation. More frequently, AMR occurs as the consequence of antibodies that are made after transplantation. AMR is increased in people with prior antigenic exposures including prior blood transfusions, child-bearing women, and the use of some mechanical support devices.[8,9]

## Chronic Lung Rejection

Chronic rejection is a terminal event for lung and heart transplants, for which there is currently no effective treatment. In the lung, chronic rejection is known as bronchiolitis obliterans syndrome (BOS). It is defined clinically by a decline in pulmonary function (reduction in forced expiratory volume in 1 s, FEV1, and/or forced midexpiratory flow rates, $FEF_{25-75}$). BOS is mediated by both immune- and nonimmune-mediated pathways. One of the known immunologic activations in BOS is the sensitization of $CD4^+$ T cells to MHC class I and class II molecules. Much of the resultant lung injury is from indirect pathway activation.[10] Antibodies directed at non-MHC antigens in the transplanted lung, such as antibodies to Kα1 tubulin or collagen V, may also induce injury and fibroproliferation.[11] Nonimmune contributors to BOS are the result of the lungs' interaction with the environment. Infections, stomach acid from gastrointestinal reflux disease (GERD), and primary graft dysfunction have also been implicated in BOS.[10]

## Chronic Heart Rejection

A diffuse concentric thickening of the coronary arteries termed coronary allograft vasculopathy (CAV) defines chronic heart rejection. Here, intimal smooth muscle proliferation causes narrowing of the coronary vessels to a point in which they can no longer supply the metabolic needs of the heart. As this is a diffuse process involving the entire coronary artery tree, unlike coronary atherosclerosis, there are no good options for stenting or using bypass grafts, making this a difficult to treat condition. Although still the target of much research, CAV is believed to be the sequella of injury to the vessel wall's endothelium. Sources of injury include immunologic (innate, T cell mediated, antibody mediated) and nonimmunologic (diabetes, obesity, hyperlipidemia,

hyperhomocysteinemia, and CMV) factors. The primary effector cell of injury is the macrophage. The macrophage secretes a variety of proinflammatory cytokines that cause tissue injury and promote smooth muscle cell proliferation in the intima.[12]

## Incidence of Rejection Events in Heart and Lung Transplantations

Over the past 20 years, a greater understanding of the immunologic response to donor organs has led to marked improvements in drugs and treatment regimens that delay graft failure, while minimizing complications of immune suppression such as renal toxicity, increased infections and elevated incidences of neoplasms. Despite that, acute rejection of both lungs and hearts still occurs with some frequency. The incidence of acute rejection occurring in the first year after lung transplantation is 36 percent.[13] For heart transplantation, ~25 percent of patients develop acute cellular rejection in the first year.[14] Most cardiac transplantation centers report AMR occurring in less than 10 percent of subjects.[15] Chronic pulmonary rejection (BOS/OB) is present in approximately 50 percent of lung transplant recipients at 5 years.[10] At 10 years, 90 percent of heart transplant recipients have developed CAV.[12]

## Histology of Pulmonary Rejection

Histology can differentiate between the acute and chronic processes that lead to pulmonary rejection. The acute processes in the lung affect the parenchyma (epithelial tissue), small blood vessels and airways. Acute rejection is noted by the presence of a mononuclear cell infiltrate in the parenchyma, a "cuffing" of the blood vessels, and pneumocyte damage (Fig. 49-4). Lymphocytic bronchiolitis is the process of rejection occurring in the airways. A working formulation for acute lung rejection has been created by the International Society of Heart and Lung Transplantation (ISHLT) (Table 49-3).[16] Chronic rejection of the lung is known as obliterative bronchiolitis and is the histologic equivalent of BOS described above. This obliterative process has a dense eosinophilic or myxoid hyaline fibrosis within the airways (Fig. 49-4).

## Histology of Cardiac Rejection

The three types of cardiac rejection (acute cellular, chronic and AMR) all have distinctive histologic appearances. Histologically, acute cellular rejection is defined by the infiltration of T cells within the myocardium and myocyte death. The extensiveness of the infiltrate and degree

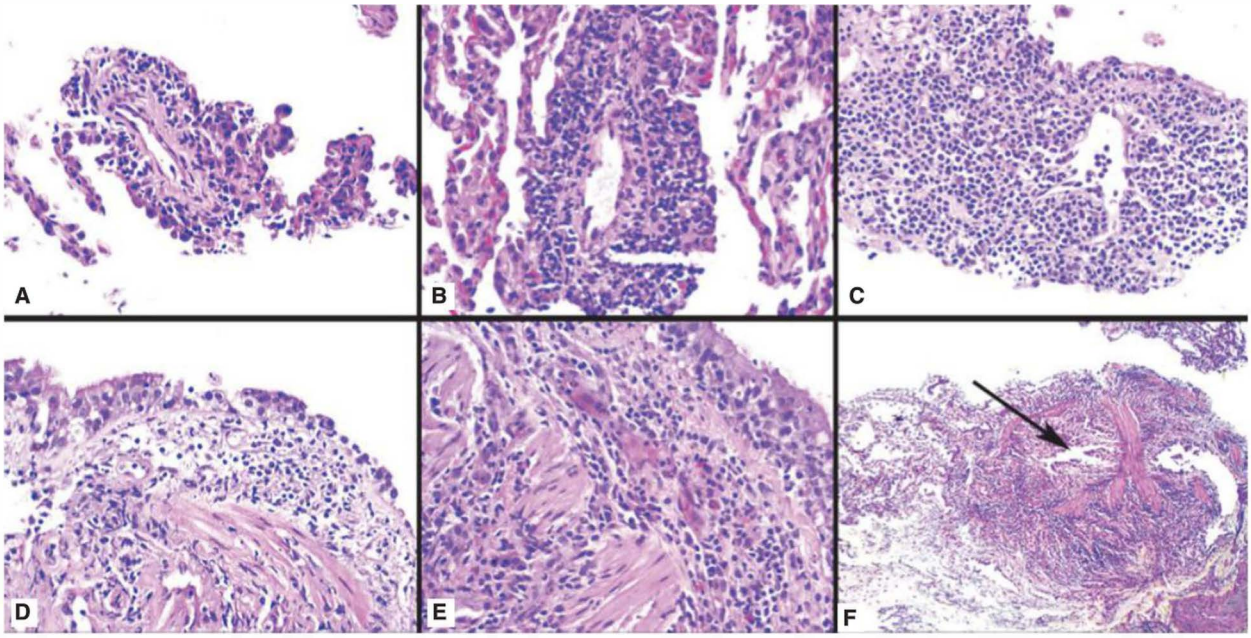



**FIGURE 49-4** Histologic findings of pulmonary rejection. **A.** Minimal (A1) parenchymal rejection showing vascular cuffing of mononuclear cells. **B.** Mild (A2) rejection showing enhanced perivascular mononuclear infiltrates without infiltration of the alveolar septa or airspaces. **C.** Moderate (A3) rejection with dense mononuclear cuffing of small blood vessels and extension of infiltrate into pervascular and peribronchioloar spaces. **D.** Low-grade (B1R) airway rejection showing a mononuclear infiltrate in the bronchiolar submucosa without epithelial damage. **E.** High grade (B2R) rejection has marked mononuclear infiltrate in the submucosa with plasmacytoid cells and eosinophils causing epithelial damage. **F.** Early bronchiolitis obliterans (C1) with fibrosis beginning to obliterate the airway resulting in luminal occlusion (arrow).

**TABLE 49-3: ISHLT Pulmonary Biopsy Grading Scheme for Acute and Chronic Rejection**

| Rejection Severity | Numerical Grade | Histologic Findings | Need to Increase Treatment? |
|---|---|---|---|
| | | **Parenchyma** | |
| None | A0 | Normal pulmonary parenchyma | No |
| Minimal | A1 | Scattered perivascular mononuclear infiltrates and vascular cuffing | Controversial |
| Mild | A2 | Frequent perivascular mononuclear infiltrates ± eosinophils ± endothelialitis, but without infiltration of the alveolar septa or air spaces | Controversial |
| Moderate | A3 | Dense mononuclear cell cuffing of small blood vessels, endothelialitis, common eosinophils, and extension of infiltrate into perivascular and peribronchiolar alveolar septa and airspaces | Yes |
| Severe | A4 | Diffuse mononuclear cell perivascular, interstitial, and air–space infiltrate and endothelialitis ± necrotic epithelial cells ± macrophages ± hyaline membranes ± hemorrhage ± neutrophils. | Yes |
| | | **Airway** | |
| None | B0 | No bronchiolar inflammation | No |
| Low grade | B1R | Mononuclear infiltrate in the submucosa without epithelial damage ± eosinophils | No? |
| High grade | B2R | Marked mononuclear infiltrate in the submucosa, eosinophils, plasmacytoid cells, epithelial damage (necrosis and metaplasia) | Yes |
| Ungradeable | BX | Not gradeable due to inadequate sample | No |
| | | **Chronic rejection** | |
| Absent | C0 | No bronchiolitis obliterans | |
| Present | C1 | Bronchiolitis obliterans | |

Data from Stewart S, Fishbein MC, Snell GI, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. *J Heart Lung Transplant* 2007;26(12):1229–1242.

of myocyte injury are highly variable, but correlate with the severity of the rejection (Fig. 49-5). The ISHLT has a working formulation for diagnosing acute cellular rejection (Table 49-4).[17] Chronic rejection is also known as transplant vasculopathy or advanced graft arteriosclerosis (AGA). This is a process of diffuse intimal thickening throughout the coronary arterial tree. Histologically, there is a concentric proliferation of vascular smooth muscle cells in the intima. Perivascular inflammation including T cells, B cells, plasma cells, and macrophages is frequently observed. The diagnosis of AMR is not made by detecting specific antibodies in the tissue, but rather is made by positive staining for the complement split products C4d and C3d as described below.

## Tools to Monitor Pulmonary Rejection

The gold standard for determining acute cellular rejection in lung transplantation is the transbronchial lung biopsy (TBB) and bronchoalveolar lavage (BAL). A TBB is performed using a flexible bronchoscope and five or more pieces of alveolated tissue are collected. These tissues and the BAL are used to differentiate between infections and rejection. Although slightly controversial, surveillance TBB are performed at most centers throughout the first year post transplantation. A typical surveillance protocol may biopsy the lung at 2, 4, and 6 weeks, then 3, 6, 12, 18, and 24 months post transplantation.[18] Emergent reasons to perform TBB/BAL are a radiographic infiltrate, a >10 percent decline in $FEV_1$, or respiratory symptoms.

Using ISHLT criteria, pulmonary rejection is evaluated separately in the parenchyma and in the airway (Table 49-3).[16] Both a hematoxylin and eosin (H&E)-stained slide and a connective tissue stain to highlight fibrosis are evaluated on each case. Acute rejection is diagnosed as either none, minimal, mild, moderate, or severe. This is dependent on the degree of mononuclear infiltrate, and the presence of eosinophils, neutrophils, and pneumocyte damage (Fig. 49-4A). Airway rejection is evaluated only in small airways (bronchioles) and is determined based upon a lymphocytic infiltrate within the mucosa and, if severe, the submucosa as well (Fig. 49-4B). All acute rejection should be distinguished from an infectious infiltrate and correlated with clinical information.

Chronic airway changes are described as obliterative bronchiolitis and represent a terminal injury to the lung. Here, dense fibrosis obliterates the airways resulting in luminal occlusion. The fibrosis can be seen in concert with myxoid material, eosinophilic change, and chronic inflammatory cells (Fig. 49-4F).

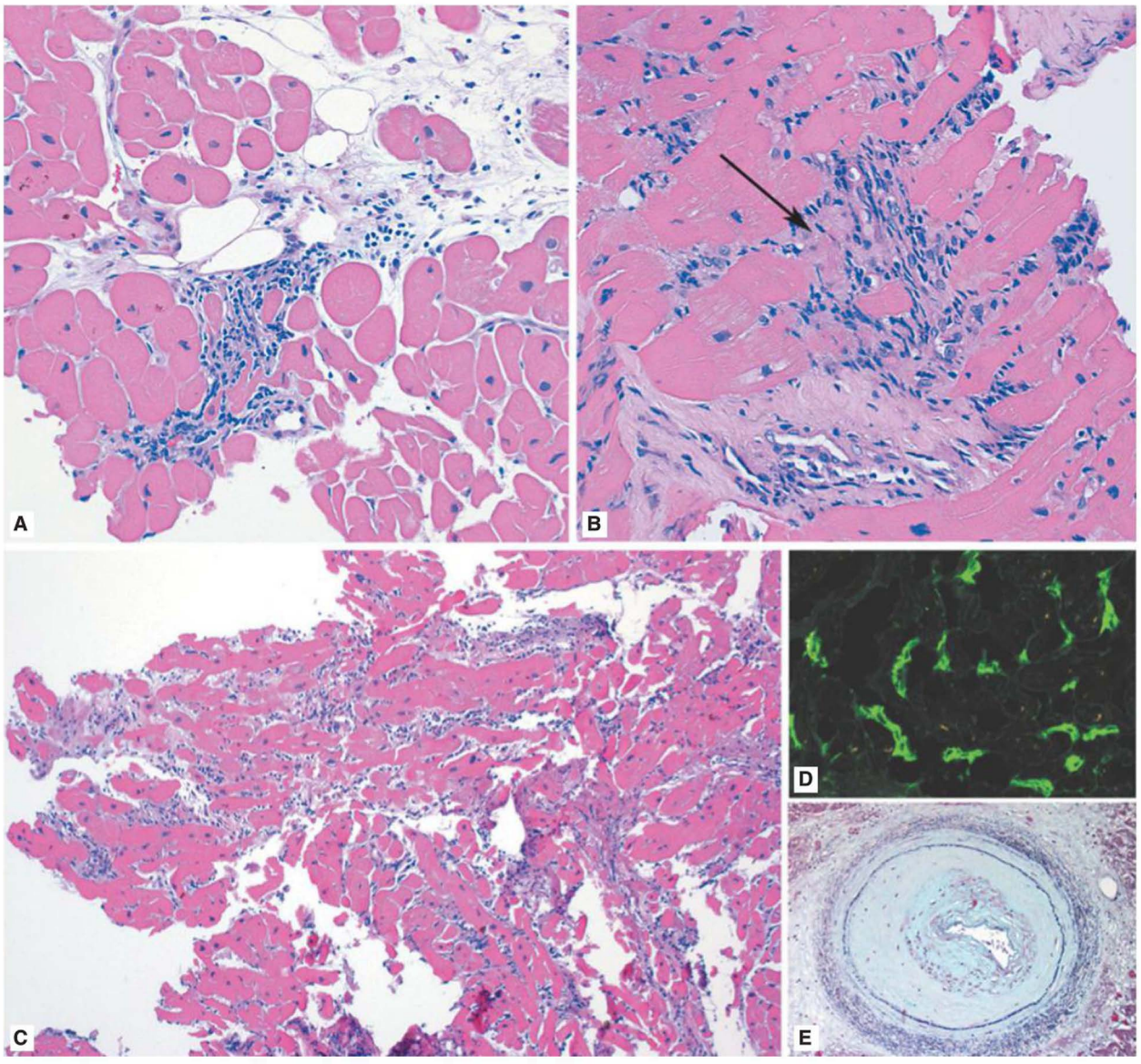



**FIGURE 49-5** Histologic findings of cardiac rejection on endomyocardial biopsy. **A.** Mild (1R) rejection showing perivascular and interstitial lymphocytes without myocyte injury. **B.** Moderate (2R) rejection showing a lymphocytic infiltrate in one of at least two distinct foci of myocyte injury (arrow). **C.** Severe (3R) rejection showing a marked lymphocytic infiltrate with diffuse, multifocal myocyte injury. **D.** AMR is present as noted by strong immunofluorescent staining of C4d in capillaries present between myocytes. **E.** Transplant vasculopathy showing concentric intimal proliferation (Movat Pentachrome).

## TOOLS TO MONITOR CARDIAC REJECTION

The gold standard for immune surveillance in the posttransplant setting remains the endomyocardial biopsy (EMBx). Newer, blood-based methods to monitor for a immunologic "fingerprint" of rejection have been tried, but have not, as yet, surpassed the sensitivity or specificity of direct tissue evaluation.[19] EMBx is performed by inserting a catheter-based Caves bioptome into the right ventricle by way of jugular vein access. Three or more pieces of myocardium are taken from the septum under radiographic guidance. This procedure is generally performed weekly for the first month, biweekly for the second month, monthly for 6 months, and bimonthly for the remainder of the first year. Biopsies are then continued on a yearly regimen or for clinical concerns.

**TABLE 49-4: ISHLT Cardiac Biopsy Grading Scheme for Acute Cellular and Antibody-Mediated Rejection**

| Rejection Severity | Numerical Grade | Histologic Findings | Need to Increase Treatment? |
|---|---|---|---|
| None | 0R | No inflammatory infiltrate | No |
| Mild | 1R | Mild interstitial and/or perivascular lymphocytic infiltrate and up to one focus of myocyte injury | No |
| Moderate | 2R | Moderate lymphocytic infiltrate ± eosinophils ± neutrophils and two or more foci of myocyte injury | Yes |
| Severe | 3R | Diffuse mixed inflammatory infiltrate with multifocal myocyte damage ± edema ± hemorrhage ± vasculitis | Yes |
| No AMR | AMR 0 | No capillary C4d staining | No |
| AMR | AMR 1 | Positive capillary C4d staining ± macrophage filling of small vascular spaces | Yes |

Data from Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant* 2005;24(11):1710–1720.

Most centers regard a proportional left ventricular ejection fraction decrease of ≥25 percent and/or other heart failure symptoms as reasons for emergent biopsy.

Acute cellular rejection is evaluated by light microscopy by a pathologist and the information is conveyed according to the ISHLT working formulation (Table 49-4).[17] If there is no infiltrate, the biopsy is said to have no rejection (0R). Mild rejection (1R) is the presence of a lymphocytic infiltrate of any degree in which there is only up to one focus with adjacent myocyte damage. Moderate rejection (2R) is the presence of a lymphocytic infiltrate and two or more foci of myocyte damage (Fig. 49-5). Severe rejection (3R) is a diffuse infiltrate with diffuse myocyte damage. In most centers, only moderate or severe rejection would result in additional immunosuppressive treatment.

AMR is evaluated by staining for the complement split product C4d and other stains including C3d. This staining can be detected by either immunohistochemistry or immunofluorescence and should be diffusely positive on capillary endothelium throughout the endocardium (Fig. 49-5). Other light microscopy findings are controversial, but the presence of macrophages filling capillaries or small venules is regarded as consistent with AMR. ISHLT guidelines indicate the presence of AMR is to be reported as AMR 1 and no AMR is to be reported as AMR 0.

Chronic cardiac rejection, CAV, is monitored by coronary angiography and the assessment of cardiac allograft function. A new scoring system has been developed to quantify the amount of CAV. The scores range between $CAV_0$ and $CAV_3$. $CAV_0$ (Not significant) denotes no detectable angiographic lesions. $CAV_1$ (Mild) indicates a lesion <50 percent of the left main coronary artery or either a primary vessel lesion or branch stenosis with narrowing of <70 percent combined with no allograft dysfunction. $CAV_2$ (Moderate) is used to indicate a ≥50 percent left main occlusion or either a single primary vessel or isolated branch stenosis in 2 systems of ≥70 percent without allograft dysfunction. $CAV_3$ (Severe) can be used to indicate both severe angiographic disease or symptomatic disease. Any $CAV_1$ or $CAV_2$ disease with allograft dysfunction (LVEF ≤45 percent) or restrictive physiology can be upscored to $CAV_3$. Also, $CAV_3$ is used when there is an angiographic lesion of the left main ≥50 percent or two or more primary vessels ≥70 percent or isolated branch stenosis ≥70 percent of all three systems.[20]

## Monitoring Donor-Specific Antibodies

In addition to immunosurveillance by evaluation of the inflammatory infiltrate in the heart and lungs, blood tests are performed to identify antibodies made by the recipient that may be directed toward the donor organ. Prior to transplant, these assays determine whether the potential recipient has been sensitized to nonself antigens through blood transfusions, prior surgeries, or pregnancies. This determination is made by evaluating the presence and titers of anti-HLA antibodies. If anti-HLA antibodies are present at high titer, desensitization protocols using plasmapheresis are used to lower these anti-HLA antibodies. After transplantation, the recipient may make antibodies directed at the donor organ resulting in AMR. These donor-specific antibodies (DSA) may be raised to a variety of nonself antigens on the heart, including endothelial proteins. At this time, however, our understanding of these nonself antibodies is incomplete and we can generally assess only anti-HLA antibodies. DSA are evaluated by solid-phase assays. State-of-the-art devices use fluorochrome-embedded beads attached to different HLA antigens. In these assays, recipient serum is tested against a full range of HLAs to determine if the recipient is making anti-HLA antibodies that may target the donor organ. Due to the conformational similarity between many HLAs, cross-reactions such as HLA B27 to HLA B2 may also trigger an AMR event.

## DRUG THERAPY FOR ACUTE REJECTION IN HEART TRANSPLANTATION

The immunosuppressive regimens used to suppress cardiac rejection generally fall into three categories: "induction," "maintenance," and "rejection" (Table 49-5).[21,22] While protocols are usually similar between centers for "maintenance" and "rejection," this is not true for "induction" protocols. An "induction" regimen begins at the time of transplantation. This regimen varies widely by both institution and patient characteristics. Some institutions perform this on all heart recipients. Others are selective. A common reason to perform "induction" therapy is to spare the kidneys

**TABLE 49-5: Antirejection Drugs**

| Drug Name | Effect | Major Side Effects | Used for |
|---|---|---|---|
| | | **Calcineurin inhibitor** | |
| Cyclosporin A | Blocks calcineurin and IL-2 activation | **Nephrotoxicity**, hypertension, hypercholesterolemia, hypertrichosis, gingival hypertrophy | Heart and lung maintenance (less favored) |
| Tacrolimus | Blocks calcineurin and IL-2 activation | **Nephrotoxicity**, hypertension, diabetes mellitus, neurotoxicity | Heart and lung maintenance (favored) |
| | | **Corticosteroid** | |
| Prednisone, Prednisolone, Methylprednisone | Suppress prostaglandin synthesis, reduce histamine/bradykinin release, downregulate cytokines | **Impaired glucose tolerance, bone density loss**, acne, hirsutism, Cushingoid features | Heart and lung maintenance and acute rejection (often tapered away in heart) |
| | | **Monoclonal antibodies to leukocytes** | |
| Basiliximab | Anti-CD25 (IL-2R) antibody, inhibits T-cell proliferation | | Heart and lung induction |
| Alemtuzumab | Anti-CD52 antibody | | Heart and lung induction (less favored) |
| Rituximab | Anti-CD20 antibody, depletes B cells | | Heart AMR |
| | | **Cell-cycle inhibitor** | |
| Azathioprine | Inhibits purine biosynthesis and lymphocyte proliferation | Leucopenia, malignancy | Heart and lung maintenance (less favored) |
| Mycophenolate mofetil (MMF) | Inhibits purine biosynthesis and lymphocyte proliferation | Diarrhea, leucopenia | Heart and lung maintenance (favored) |
| | | **Antithymocyte globulin (ATG)** | |
| Polyclonal anti-lymphocyte preparation (ATGAM) | T-cell cytotoxic | **Cytokine release syndrome**, leucopenia, thrombopenia, allergic reaction, infections | Heart induction |
| Anti-thymocyte globulin (Thymoglobulin) | T-cell cytotoxic | Infections, thrombopenia | Heart induction and acute rejection (less favored) |
| | | **mTOR inhibitor** | |
| Sirolimus | Prevents T-cell proliferation | **Hyperlipidemia**, delayed wound healing, pneumonitis, thrombocytopenia, arthralgia | Some use in replacing calcineurin inhibitors/ may delay CAV and BOS |
| Everolimus | Prevents T-cell proliferation | **Hyperlipidemia**, delayed wound healing, thrombocytopenia, arthralgia | Some use in replacing calcineurin inhibitors/ may delay CAV and BOS |
| Muromonab-CD3 (OKT3) | Blocks T-cell binding to APCs | **Cytokine release syndrome**, lymphoproliferative disorders, induction of AMR, procoagulation effect | Lung induction (less favored) |
| | | **Immunoglobulin** | |
| Intravenous immunoglobulin (IVIg) | Interferes with $F_c$ receptors in reticuloendothelial system | | Heart AMR |

Data collected from Korom S, Boehler A, Weder W. Immunosuppressive therapy in lung transplantation: State of the art. *Eur J Cardiothorac Surg* 2009;35(6):1045–1055. Hunt SA, Haddad F. The changing face of heart transplantation. *J Am Coll Cardiol* 2008;52(8):587–598. Knoop C, Haverich A, Fischer S. Immunosuppressive therapy after human lung transplantation. *Eur Respir J* 2004;23(1):159–171.

from calcineurin inhibitors especially in patients with diabetes or any level of renal dysfunction. Other populations that more frequently have "induction" therapy are young females, presensitized patients, ventricular assist device recipients, and individuals with prior open chest surgery. The purpose of this regimen is to markedly suppress early cardiac rejection and try to increase tolerance of the new organ. This regimen is comprised of IL-2R antagonists or drugs that kill lymphocytes (ATGAM or thymoglobulin).

A "maintenance" regimen then follows the "induction" regimen and is designed to balance the need for continued immunosuppression to maintain graft function, while limiting the risk of infections and neoplasm. This therapy is comprised of a calcineurin inhibitor, an antiproliferative agent and a steroid that is generally tapered away. Patients who have evidence of cellular rejection by EMBx will undergo a short course of a "rejection" regimen that will further suppress them beyond their normal "maintenance" regimen. The change in medications is dependent upon the severity of the rejection and can be as minimal as a course of corticosteroids, increased doses of current medications, or an addition of an antilymphocyte agent.

## THERAPY FOR ANTIBODY-MEDIATED REJECTION IN HEART TRANSPLANTATION

Traditional immunosuppressive therapy is generally not effective in treating AMR. Patients diagnosed with AMR based upon positive C4d, DSA, and clinical symptoms have therapies targeted toward reducing antibodies and depleting B cells. These include plasmapheresis to eliminate circulating antibodies, intravenous immunoglobulins (IVIg) to inhibit residual antibodies, and possibly rituximab to deplete the B-cell population (Table 49-5). Due to the limited experience with AMR at most centers, treatments may vary widely between centers.

## DRUG THERAPY FOR ACUTE REJECTION IN LUNG TRANSPLANTATION

Similar to cardiac transplantation, immunotherapies for lung transplantation also can be considered "induction," "maintenance," and "rejection" (Table 49-5). Due to the overall fewer numbers of lung transplants that are performed relative to heart transplantations, consensus has not been reached on treatment regimens. Induction therapy is reported to occur in >50 percent of lung recipients.[13] A variety of therapies are used including ATGAM, tacrolimus, alemtuzumab, basiliximab, and daclizumab, with the last two being the most commonly used. For maintenance, three drug classes are commonly used: a calcineurin inhibitor, a cell-cycle inhibitor and steroids. The specific drug from each class along with relative dosing is variable among institutions. Unlike heart transplantation, steroid withdrawal is not widely performed. For acute rejection, intravenous corticosteroid pulses for 3 to 5 days and a temporary increase in dosing levels of the maintenance regimen are used.[23]

## SPECIAL CONSIDERATIONS

### ABO Incompatible Heart Transplantation

Due to a shortage of donors in the pediatric population, the use of ABO incompatible heart transplantation has been developed. A window of opportunity occurs in the first 6 months of life before "natural antibodies" to blood group A or B are generated due to cross-reactive carbohydrates on normal gut flora. This accounts for the lack of hyperacute rejection. The unanticipated finding has been the apparent establishment of tolerance to blood group antigens by the presence of the transplanted heart. For example, a patient of blood group O, who receives a blood group A heart develops antibodies to blood group B, but not to A.[24] Ten years of registry data indicates that survival of ABO incompatible heart transplant patients is comparable to ABO matched recipients, suggesting good long-term outcomes of this procedure.[25] ABO incompatible heart transplants have been reported in a few adults who have low titers of isohemagglutinins.[26]

### Combined Heart and Lung Transplantation

Some patients develop both heart and lung failure and need replacement of both organs. The primary causes are congenital heart disease, primary pulmonary hypertension, cystic fibrosis, and other rare and miscellaneous disorders. The immunosuppression protocols for lung transplantation are typically followed in these patients. Rejection occurs almost exclusively in the lungs of these individuals, and not surprisingly, pulmonary complications are more prevalent than cardiac complications for these individuals and are a more likely cause of mortality.[13]

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## THE IMMUNOBIOLOGY OF THORACIC TRANSPLANTATION BOARD REVIEW QUESTIONS (CHAPTER 49)

1. Which is true regarding the mechanism of indirect allorecognition pathway?
   A. MHC class I and II molecules on donor APCs present nonself antigen to $CD4^+$ T cells.
   B. Necrotic nonself cellular debris is phagocytized by APCs, which display the nonself antigen through MHC class II molecules for $CD4^+$ T cells.
   C. Exosomes containing MHC move from donor APCs to recipient APCs, which display nonself antigen to $CD4^+$ T cells.
   D. Necrotic transplanted cells become coated in complement, which activates macrophages.
   E. Bacterial infections in the transplanted organ activate TLR on neutrophils, which initiate signaling activating a T-cell response.

2. Which of the following is not a pattern recognition receptor of the innate immune system?
   A. CRP
   B. MBL
   C. Cyclooxygenase 1 (COX1)
   D. Complement C1q
   E. TLR1

3. What is the most appropriate therapy for a lung transplant biopsy graded as parenchymal moderate rejection (A3) with no bronchiolar inflammation (B0)?
   A. No treatment
   B. Two-week course of ATGAM
   C. Intravenous corticosteroid pulse
   D. IVIg with or without rituximab
   E. Basiliximab (anti-CD25 antibody) treatment

4. What is most appropriate therapy for a heart transplant biopsy graded as mild (1R) with no evidence of antibody mediated rejection (AMR0)?
   A. No treatment
   B. Two-week course of ATGAM
   C. Intravenous corticosteroid pulse
   D. IVIg with or without rituximab
   E. Basiliximab (anti-CD25 antibody) treatment

5. Which of the following is characteristic of moderate or severe cardiac rejection?
   A. Multiple foci of myocyte injury
   B. Positive staining for complement C4d
   C. Heavy infiltrate of lymphocytes interdigitating between myocytes
   D. Macrophages filling arterioles and capillaries
   E. Plugging of small blood vessels with thrombin

## ANSWERS

1. **Answer: B.** The indirect pathway involves necrotic nonself cellular debris that is phagocytized by APCs, which display the nonself antigen through MHC class II molecules for $CD4^+$ T cells. The direct pathway involves MHC class I and II molecules on donor antigen presenting cells (APCs) that present nonself antigen to $CD4^+$ T cells. The semidirect pathway requires exosomes containing MHC to move from donor APCs to recipient APCs, which display nonself antigen to $CD4^+$ T cells. Complement and bacterial infections do not contribute to the allorecognition pathways.
2. **Answer: C.** COX1 is not a pattern recognition receptor. CRP, MBL, C1q, and TLR1 are all part of the innate immune system.
3. **Answer: C.** A lung transplant recipient with moderate rejection on biopsy should be treated with steroid pulse therapy. No or mild rejection can be observed closely without increasing therapy. Antibody therapy is typically reserved for more severe forms of rejection.
4. **Answer: A.** Mild (1R) rejection on endocardial biopsy can be treated conservatively with no additional therapy. Moderate rejection is generally treated with steroid therapy, while more severe forms of rejection are treated with antibody therapies.
5. **Answer: A.** The presence of multiple foci of myocyte injury is diagnostic of moderate or severe rejection when compared with no or mild rejection. Complement staining is used to differentiate between AMR0 and AMR1. Lymphocyte infiltration, macrophage presence, and thrombin plugging are not specific to moderate or severe rejection.

# 50 Cardiac Transplantation

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**KEY CONCEPTS**

- Epidemiology
  - Heart failure increases as the population ages and becomes increasingly obese. It can be acute or chronic, and systolic or diastolic.
- Pathophysiology
  - Heart failure may result from untreated hypertension or a myocardial infarction. Viruses may have caused idiopathic dilated cardiomyopathies. Hypertrophic cardiomyopathy is less common. Infiltrating cardiomyopathies also occur.
- Clinical features
  - Left-heart failure is manifested by shortness of breath, cough, and fatigue. Right-heart failure is responsible for right upper quadrant abdominal discomfort from a congested liver and peripheral edema. Ascites occurs later.
- Diagnostics
  - Patient with heart failure are evaluated by echocardiography, and right and left cardiac catheterization. Coronary angiography is still the gold standard for evaluating coronary artery disease.
- Treatment (medical/surgical)
  - Heart transplantation is reserved for patients who are failing medical management and are not thought to have a life expectancy of greater than 2 years. It can be done after the patient has been bridged with a left ventricular assist device (LVAD).
- Outcomes/prognosis
  - The median survival after cardiac transplantation is 10 years. The mortality rate after 1 year is 3 to 4 percent/year.

Theodore Billroth could never have imagined that one day cardiac transplantation would be a viable clinical entity. First, surgical techniques needed to be developed. The operation had to be reproducible. Myocardial protection was crucial. The heart was not so important to the organism that the organism would not reject it.[1] Over the course of the 20th century cardiac transplantation evolved from an experimental heterotopic model, where a puppy heart was placed in the neck of an adult mongrel dog, to an orthotopic operation where over 4400 heart transplants were performed in 1994.[2] Unfortunately, the number of donor hearts are not such that everyone with end-stage heart failure can be treated with transplantation. This has given rise to the evolution of mechanical circulatory assist devices that can be placed in patients to at least postpone cardiac transplantation.

Since cardiac transplantation became a clinical entity on December 3, 1967, well over 89,000 heart transplants have been performed.[3] Records have been collected by the International Society for Heart and Lung Transplantation in the form of a Scientific Registry since 1983. It has been interesting to watch the field evolve over the past 46 years. Over that course of time, decreased lengths of stay and increased ages of the donor and recipient have been realized.[4] Recipient waiting list times have increased dramatically, as have times before first rejection episodes.

## HISTORICAL BACKGROUND

Alexis Carrel and Charles Guthrie performed the first documented cardiac transplant in 1905 at the University of Chicago. The heart of a small dog was transplanted into the neck of an adult mongrel dog. Mann performed a heterotopic cardiac transplant in 1933.[5] A canine heart was sewn into the carotid-jugular circulation. The explanted heart revealed dense infiltration of the heart by lymphocytes, large mononuclear cells, and polymorphonuclear cells. It was cellular rejection.

By the late 1950s, experimental cardiac transplantation, both autografts and homografts, were being performed in the laboratory at Stanford. Using local hypothermia, orthotopic transplantation in dogs was successfully performed

in 1959. Richard Lower reported successful experiments in cardiac transplantation at the 1960 Surgical Forum of the American College of Surgeons.[6] By 1965, long-term survival of orthotopic cardiac transplantation was achievable in dogs. Electrocardiography was used to guide treatment of rejection. In the laboratory, using local and systemic hypothermia for myocardial protection, successful transplantation of the canine heart was achievable after 7 h of ischemia.

James Hardy transplanted a chimpanzee heart into a human as a desperate measure in 1964. Christiaan Barnard performed the first human-to-human heart transplant in Cape Town, South Africa, on December 3, 1967. The first cardiac transplant at Stanford University was performed on January 6, 1968. A number of programs throughout the world subsequently performed cardiac transplants between 1967 and the early 1970s with relatively poor outcomes; 5-year survival rates hovered around 40 percent. By the early 1970s Stanford and the Medical College of Virginia were the only two programs still actively conducting clinical cardiac transplant programs, with Stanford taking the lead in conducting basic and clinical transplant research. In 1971 Philip Caves, a British American research fellow, along with Margaret E. Billingham, developed a technique for the interpretation of percutaneous transvenous endomyocardial biopsies.[7] This important advance provided clinicians with the ability to better identify and treat cardiac allograft rejection.

By December 1980, the immunosuppressant cyclosporine was introduced into clinical use. By 1984, cyclosporine, corticosteroids, and azathioprine were combined as "triple drug therapy." This proved to be an effective immunosuppression regimen that was adopted widely.[8] Cardiac transplantation in children began in 1984.[9] By the 1990s, it was clear that induction therapy could be added to triple drug therapy in order to delay early acute rejection.[10] Chronic allograft rejection, manifested primarily as graft atherosclerosis, became the bête-noire of clinical cardiac transplantation.

The mid 1990s also saw the evolution of medical devices directed toward the treatment of heart failure, specifically ventricular assist devices and more reliable pacemakers and automatic implantable defibrillators. Over the past 20 years, ventricular assist devices have developed into effective bridges to transplantation or so-called "destination therapy" for end-stage heart failure.

## RECIPIENT SELECTION

The potential cardiac transplant recipient must undergo a battery of tests to determine whether or not he or she is an appropriate transplant candidate. Initially, a thorough history and physical examination, standard laboratory tests, plain chest radiography, and pulmonary function tests are obtained. Cardiac function is evaluated by electrocardiography, echocardiography, right and left heart catheterization, endomyocardial biopsy, and peak exercise oxygen consumption measurements.

**TABLE 50-1: Relative Contraindications for Cardiac Transplantation**

| |
|---|
| Age (70) |
| Active myocarditis |
| Graft failure due to acute rejection |

Screening tests include: stool guaiac, mammography for women, prostate-specific antigen screening for men, Papanicolaou smear for women, bone densitometry, and a carotid duplex study. Occult infectious diseases are ruled out with serologies for hepatitis B and C, HIV, HTLV1, and HTLV2, cytomegalovirus, Toxoplasma, Epstein–Barr virus, syphilis, and tuberculosis. Pretransplant data also includes blood type and antibody screening, HLA–DR typing, panel reactive antibody (PRA) screening, and a 12-h urine collection to measure creatinine clearance and total protein.[11]

Idiopathic and ischemic cardiomyopathies each comprise about 45 percent of the diagnoses among adult cardiac transplant recipients. The remaining diagnoses consist of valvular and congenital disease. Most recipients present in New York Heart Association class III or class IV heart failure refractory to medical therapy. Some patients suffer from intractable ischemia that is not amenable to catheter intervention or surgical revascularization. Still other patients present with intractable ventricular arrhythmias refractory to conventional therapies.

There have been recent advances in medical therapies for heart failure. In 2001, the COPERICUS trial found that patients with severe heart failure treated with Carvedilol had a reduced 1-year mortality of 11 percent compared with the placebo group who had a 1-year mortality of 19 percent. Waiting list mortality has decreased from about 32 to 17 percent due to the expanded use of ventricular assist devices and earlier consideration for cardiac transplantation.

There are relative, temporary, and absolute contraindications to cardiac transplantation (Tables 50-1–50-3). Severe pulmonary hypertension with pulmonary vascular resistances in excess of 4 Wood units or transpulmonary gradients greater than 15 mm Hg can lead to acute right ventricular failure of the newly implanted donor heart. Irreversible renal or hepatic dysfunction represent absolute contraindications to cardiac transplantation, although multiorgan transplants (e.g., heart–kidney, heart–liver) have been performed with some success.[12,13]

**TABLE 50-2: Temporary Contraindications for Cardiac Transplantation**

| |
|---|
| Active infection |
| Active peptic ulcer disease |
| Diverticulitis |
| Recent pulmonary/cerebral emboli |
| Symptomatic cholelithiasis |

**TABLE 50-3: Absolute Contraindications for Cardiac Transplantation**

| |
|---|
| Positive prospective crossmatch |
| Irreversible pulmonary hypertension (PVR ≥5 Wood units) |
| Malignancy |
| Severe peripheral or cerebral vascular disease |
| Irreversible renal dysfunction (creatinine clearance <40 mL/min) |
| Irreversible hepatic dysfunction |
| Severe obstructive or restrictive lung disease |
| Coexisting systemic disease |
| Diabetes mellitus with end-organ damage |
| Morbid obesity (≥30% predicted ideal weight) or BMI greater than 35 |
| Severe cachexia |
| Ongoing tobacco use or drug addition |
| Ongoing alcohol abuse |
| Noncompliance with medications |
| Inability to fully understand procedure and participate in follow-up care |

All potential recipients are screened for occult malignancy. Severe peripheral vascular disease and diabetes resulting in end-stage organ damage are also contraindications. Primary diseases of the heart such as amyloidosis or sarcoidosis and giant cell myocarditis can be contraindications. Relative contraindications to transplantation include age greater than 70 years, obesity greater than 140 percent ideal body weight, severe osteoporosis, a history of substance abuse, and psychiatric disorder. A history of medical noncompliance and lack of social support are other potential contraindications.

Once a patient has been listed for transplantation, he or she should be followed by a cardiologist at the transplant center, usually every 3 months. Cardiac rehabilitation is also an important tool during this waiting time. Patients suffering from severe heart failure may require intravenous inotropic support (e.g., dobutamine). Milrinone, a phosphodiesterase inhibitor with inotropic and vasodilatory affects, is also an effective inotrope, especially for right heart failure.

A number of devices have been used as adjuncts to medical therapy. Intra-aortic balloon pumps have provided circulatory support for as long as 2 to 3 weeks prior to heart transplantation. This appears to be most effective in patients with ischemic cardiomyopathies. For patients with severe refractory ventricular failure, a left ventricular assist device (LVAD) or right ventricular assist device may be necessary. INTERMACS is a database recently developed to track all patients requiring ventricular assist devices.[14]

The REMATCH trial, published in 2001, compared 1- and 2-year survival rates of heart failure patients who were not candidates for cardiac transplantation and were treated with either medical therapy or LVAD implantation.[15] The investigators reported a 25-percent 1-year survival rate and 8-percent 2-year survival rates in the medical therapy group compared with a 52-percent 1-year survival rate and a 23-percent 2-year survival rate in the LVAD group. The use of ventricular assist devices for bridging to transplantation is increasing.

## DONOR MANAGEMENT AND SELECTION

As with any organ donor assessment, the two most important goals are to prevent disease transmission from the donor to the recipient and to obtain a graft that will function appropriately. Donor heart exclusion criteria include (1) malignancy with extracranial metastatic potential, (2) systemic sepsis or endocarditis, (3) significant coronary artery disease, (4) anatomic heart disease that will shorten the recipient's expected life span, and (5) poor ventricular function.

Ideally, the cardiac donor is less than 55 years of age with no history of chest trauma or cardiac disease. There should be no prolonged hypotension or hypoxemia. Hemodynamically, the mean arterial blood pressure should be maintained above 60 mm Hg and the CVP between 8 and 12 mm Hg. Inotropic support requirements should be less than 10 mg/kg/min of dopamine or dobutamine. Normal electrocardiograms and echocardiograms should be verified. Risk factors for coronary artery disease mandate normal coronary angiography. All pertinent serologies should be negative.

Due to the relative donor organ shortage, there has been a trend toward liberalizing certain donor selection criteria. Expanded organ criteria include the use of older donors and allowing for longer ischemic times. Donors with mild left ventricular hypertrophy, mild valvular abnormalities, or mild coronary artery disease have been used with success.[16] Hearts that have experienced cardiac arrest have also been used.

Most organ donors who have suffered acute brain injury will display some hemodynamic instability. Neurogenic shock can cause excessive fluid losses and bradycardia. Careful fluid management is necessary. It is also important to wean inotropic support as much as possible. Blood transfusion is also used sparingly to maintain a hematocrit of at least 30 percent. If possible, cytomegalovirus negative and leukocyte-filtered blood should be used. Donors may require intravenous vasopressin to keep up with the excessive urine losses caused by diabetes insipidus.

A single echocardiogram may show decreased ventricular function related to brain death, so serial echocardiograms may show functional recovery. The Papworth group has instituted a very aggressive protocol for donor management.[17] Using pulmonary arterial catheter monitoring, donors are managed by a cardiac trained anesthetist. Hormonal therapy includes the use of thyroxine, cortisol, antidiuretic hormone, and insulin. If a left ventricular ejection fraction of greater than 45 percent is attained, the organ should be usable.

In the United States, organ allocation is governed by the United Network for Organ Sharing (UNOS). Heart allocation takes into consideration medical urgency, time on the waiting list, and blood type. The medical urgency categories

**TABLE 50-4: UNOS Medical Urgency Status Categories**

| Status Level | Category |
|---|---|
| 1A | Patient is listed at the transplant hospital and has one of the following devices or conditions:<br>1. Left and/or right ventricular assist device<br>2. Total artificial heart<br>3. Intra-aortic balloon pump<br>4. Extracorporeal membrane oxygenation<br>5. Mechanical circulatory support with evidence of significant device-related complications<br>6. Mechanical ventilation<br>7. Continuous infusion of a single high-dose intravenous inotrope.<br>8. Life expectancy <7 days |
| 1B | One of the following devices or conditions:<br>1. Left or right ventricular assist device<br>2. Continuous infusion of intravenous inotropes |
| 2 | All other actively listed patients |
| 7 | Patient is temporarily removed from active waiting list |

include status 1A, 1B, 2 and 7 (Table 50-4). The allocation algorithm is also modified by age so that adolescent donor hearts are preferentially used by pediatric recipients. Organs are initially allocated locally, then regionally.

Prospective recipients and donors must be ABO blood type compatible, except in infants. As far as size is concerned, typical acceptable donor weight ranges are between 70 and 130 percent of the recipient weight.[18] For recipients with moderately elevated pulmonary vascular resistance, it is often prudent to use a larger donor. Using smaller hearts in a heterotopic position for larger recipients has fallen out of favor. The donor team should have a checklist to ensure completeness of the donor organ assessment (Table 50-5).

There are certain strategies that have been used to improve preservation of the heart during organ retrieval. This has included the use of hypothermia, cardioplegia, and various preservation solutions. The heart is maintained in a hypothermic environment between 4°C and 8°C to reduce the rate of myocardial metabolism. Cardioplegia is used to arrest the heart. Adequate decompression of the ventricles during the organ retrieval limits injury to the heart during the actual procurement. The heart is stored in either cold saline or a variety of preservation solutions. Most preservation solutions were designed for perfusion or storage of abdominal organs.[19] Many also contain antioxidant additives to help prevent reperfusion injury. Cardiac preservation is usually limited to 4 to 6 h of cold ischemia time. Longer ischemia times have affected recipient survival. This is an area of active research.

**TABLE 50-5: Checklist for Donor Procurement Team**

1. Donor properly identified using UNOS donor-specified ID
2. ABO compatibility of donor and recipient confirmed
3. Donor-specific documentation re: local definition of brain death
4. Donor chart review
5. Donor EKG, ECG
6. Donor echo
7. Operating room assessment

## OPERATIVE TECHNIQUES

### Cardiac Allograft Procurement

Donor cardiac procurement is performed through a complete median sternotomy. The pericardium is opened widely and the edges are suspended. Care is taken not to enter either pleural space should the lungs be infected. The heart is inspected for any signs of trauma, infection, or congenital anomalies. Overall contractility of both the right and left ventricles is appreciated. The coronary arteries are palpated to rule out any evidence of coronary artery disease. The ascending aorta is separated from the pulmonary artery. The superior vena cava (SVC) is mobilized circumferentially up to and beyond the level of the azygos vein, and encircled with two heavy ties of 0 silk sutures. The inferior vena cava likewise is mobilized circumferentially and surrounded with a vessel loop.

At least 300 units of heparin/kg of donor weight are administered intravenously to the donor. A cardioplegia needle is inserted into the ascending aorta. Venous return to the heart is interrupted by dividing the SVC between two secured ties. The IVC is divided flush with the diaphragm. The tip of the left atrial appendage is amputated. The ascending aorta is cross-clamped and approximately 2 L of cold cardioplegia is administered into the ascending aorta. In children, 50 mL/kg of cardioplegia is appropriate. Ice slush is immediately poured into the pericardial space and onto the heart to provide rapid topical cooling. Once a complete cardiac arrest is achieved and all of the cardioplegia has been administered, the topical ice slush is removed from the pericardial space and the heart is excised in a expedient fashion. First, the pulmonary veins are divided flush with the pericardium. The aorta is divided as distally as possible, usually at the take off of the innominate artery, and the main pulmonary artery is divided at its bifurcation. The heart is then placed in a secure Teflon container filled with cold saline or other preservation solution and then placed in a cooler filled with ice.

Ideally, the donor cardiac graft should be reperfused in the recipient within 4 to 6 h of its excision from the donor.[20] Ischemic times greater than 4 h have resulted in decreased recipient survival. If the recipient requires reconstruction of both pulmonary arteries, then the branch pulmonary arteries are divided at the level of the pulmonary hilum. Additional length of the ascending aorta may be required for recipients

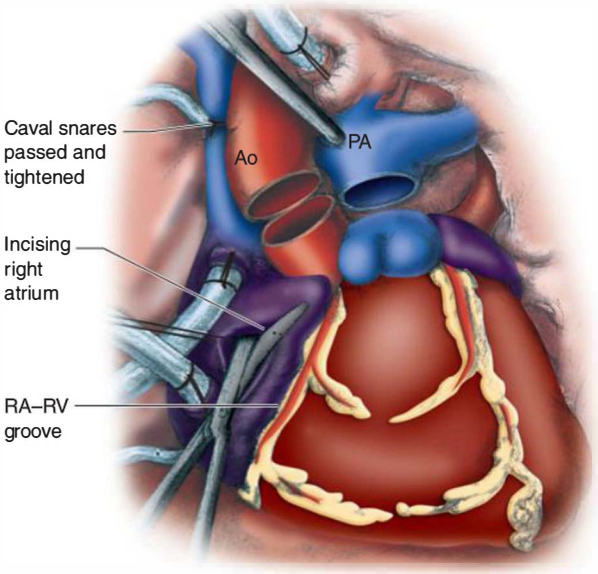



**FIGURE 50-1** Excision of the recipient heart. (Reproduced with permission from Shumway SJ. *Thoracic Transplantation*. In: Shumway SJ, Shumway NE (eds). Boston: Blackwell Science, Inc., June 1995. Fig. 15-3.)

with hypoplastic left heart syndrome or with L-transposition of the great vessels.[21]

## Recipient Cardiectomy

If the recipient has undergone previous cardiac surgery, it is helpful to obtain a CT scan of the chest to demonstrate the proximity of the heart or other critical structures (e.g., LVAD outflow graft) to the undersurface of the sternum. All recipients are fully heparinized. Bicaval cannulation with caval snares and a standard aortic cannula are used. The SVC is cannulated high enough to facilitate the SVC anastomosis. The recipient is then placed on total cardiopulmonary bypass and an aortic cross-clamp is placed across the ascending aorta. When bicaval anastomoses are being performed, the recipient cuffs are fashioned at the level of the superior and inferior vena cava after the interatrial groove is developed in order to facilitate excision of the right atrium. Generally, the native right atrium is open anteriorly and the right atriotomy is extended superiorly, trimming off the right atrial appendage (see Fig. 50-1). The right atriotomy is then extended inferiorly into the coronary sinus. Each great vessel is divided above its semilunar valves. The cardiectomy continues by opening the roof of the left atrium. The left pulmonary veins are identified and the left atriotomy continues along the atrioventricular groove. The pericardial sac is irrigated with cold saline solution to remove debris. The left atrial cuff is further trimmed as needed. In patients with ischemic cardiomyopathy, the epicardial portion of the left atrial cuff may require cauterization.

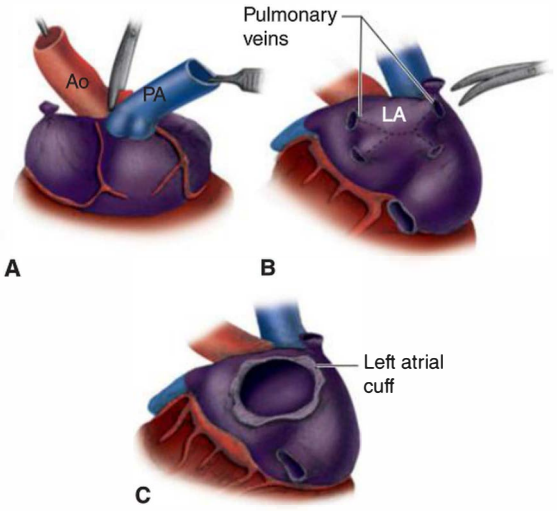



**FIGURE 50-2** Preparation of the donor heart. (Reproduced with permission from Shumway SJ. *Thoracic Transplantation.* In: Shumway SJ, Shumway NE (eds). Boston: Blackwell Science, Inc., June 1995. Fig. 15-2.)

## Donor Graft Implantation

After removing the donor heart from its sterile container, the aorta and pulmonary arteries are separated (see Fig. 50-2). The donor pulmonary artery is trimmed just proximal to its bifurcation. The donor aorta is likewise trimmed just proximal to the takeoff of the innominate artery. The pulmonary veins are identified and connected in a cross-like manner. The left atrial cuff is then trimmed appropriately. The mitral valve is inspected. Next, the inferior vena cava is located. Any patent foramen ovale is identified and closed. If biatrial anastomoses are planned, the inferior vena cava is opened curvilinearly toward the right atrial appendage to avoid the sinus node. The SVC is closed circumferentially with two layers of running 4-0 polypropylene suture. The donor heart is then kept in cold saline solution until implantation. Retrograde cold blood cardioplegia may be delivered via the coronary sinus when the ischemic time exceeds 4 h.

Implantation commences with the left atrial anastomosis. The donor heart is typically wrapped in a cold saline sponge. The donor and recipient left atrial cuffs are anastomosed in an end-to-end fashion with a running 3-0 polypropylene suture (see Fig. 50-3). Just before this suture line is completed, the left atrium is filled with cold saline solution, and the suture line is secured. Some surgeons prefer to leave a vent in the left atrium in order to keep the heart decompressed. When bicaval anastomoses are planned, the IVC anastomosis is performed in an end-to-end fashion with a running 4-0 polypropylene suture followed by an end-to-end SVC anastomosis. If biatrial anastomoses are planned, the right atrial cuff anastomosis is performed at this time. Finally, the main pulmonary arterial and aortic anastomoses are performed in an end-to-end fashion with running

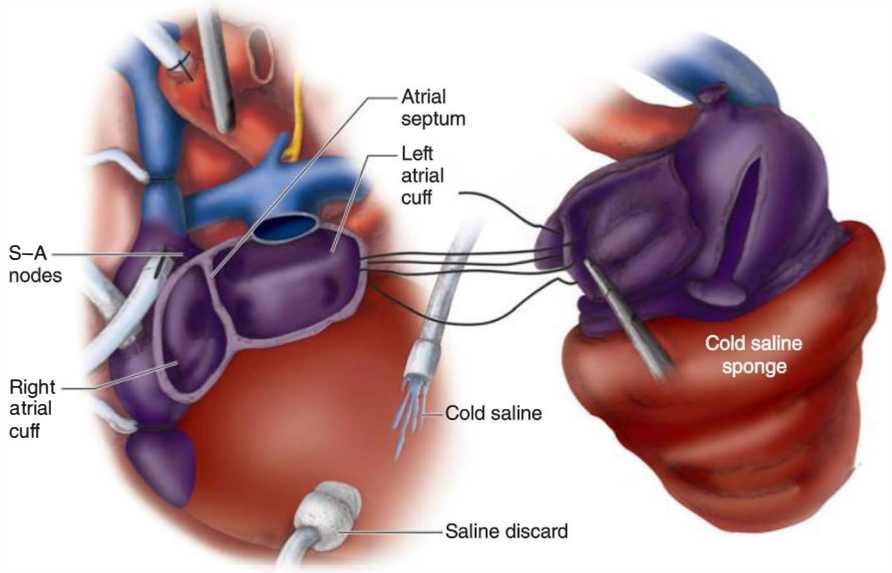



**FIGURE 50-3** Performing the left atrial anastomosis. (Reproduced with permission from Shumway SJ. *Thoracic Transplantation*. In: Shumway SJ, Shumway NE (eds). Boston: Blackwell Science, Inc., June 1995. Fig. 15-4.)

4-0 polypropylene sutures (see Fig. 50-4).[22] Care must be taken to fashion the pulmonary arteries to the appropriate length to avoid kinking. Kinking of a reconstructed pulmonary artery can cause right heart failure postoperatively. Active warming of the recipient begins as the great vessel anastomoses are being performed.

Prior to release of the aortic cross-clamp, it is advisable to place a root vent in the ascending aorta to ensure adequate de-airing. The recipient receives a dose of intravenous steroids prior to release of the aortic cross-clamp. In addition, it is helpful to start isoproterenol at 0.01 to 0.02 μg/kg/min as a chronotrope. Intravenous epinephrine and milrinone are also excellent perioperative drugs for the newly reperfused donor organ. Once the aortic cross-clamp is released, a period of allograft reperfusion is important to resuscitate the graft. Once the heart is beating vigorously and the patient is warm, the vent in the left atrium is removed. The aortic root vent is left in place until, by transesophageal echocardiography, it is clear that adequate de-airing has been performed. The recipient is then carefully separated from cardiopulmonary bypass. Transesophageal echocardiography is helpful in evaluating graft performance. Two temporary atrial pacing wires are placed on the donor right atrium, and two temporary ventricular pacing wires are placed on the donor right ventricle.

## POSTOPERATIVE MANAGEMENT

### ICU Care

The principles of posttransplant care are similar to those used in the routine postoperative care of cardiac surgical patients. Hemodynamic monitoring is used, including measurements of systemic arterial pulmonary arterial and central venous pressures measurements, cardiac output and index, urine output, and mixed venous saturation ($Svo_2$). Optimizing gas exchange is important and particular attention is paid to keeping arterial $Pco_2$ levels relatively low and avoiding a base deficit, particularly in the setting of pulmonary hypertension. Chest tube output, coagulation parameters, and serial hemoglobin levels are closely monitored. Significant blood loss is replaced with packed red blood cell transfusions. Any coagulopathy is corrected. Serum hemoglobin levels are kept above 9 g/dL to promote adequate tissue oxygen delivery capacity. Urine output is closely monitored and diuretics are used for volume overload. The urine output is nominally maintained at greater than 30 mL/h.

The following hemodynamic parameters are considered physiologic and optimal: systemic blood pressure greater than 90 mm Hg, mean arterial pressure greater than 60 mm Hg, central venous pressure between 5 and 18 mm Hg, pulmonary artery pressure less than or equal to one-third of the systemic blood pressure, cardiac indices greater than 2 L/min/$m^2$, and $Svo_2$ levels greater than 65. Ventilator weaning is begun as soon as the patient is awake and determined to be hemodynamically stable without evidence of mediastinal bleeding.

Several unique physiologic features of a cardiac allograft should be considered in the early postoperative period.[23] One distinct characteristic of the transplanted heart is that it is totally denervated, which may result in a reduction in its intrinsic heart rate. Consequently, a chronotropic catecholamine agent is routinely used in the early postoperative

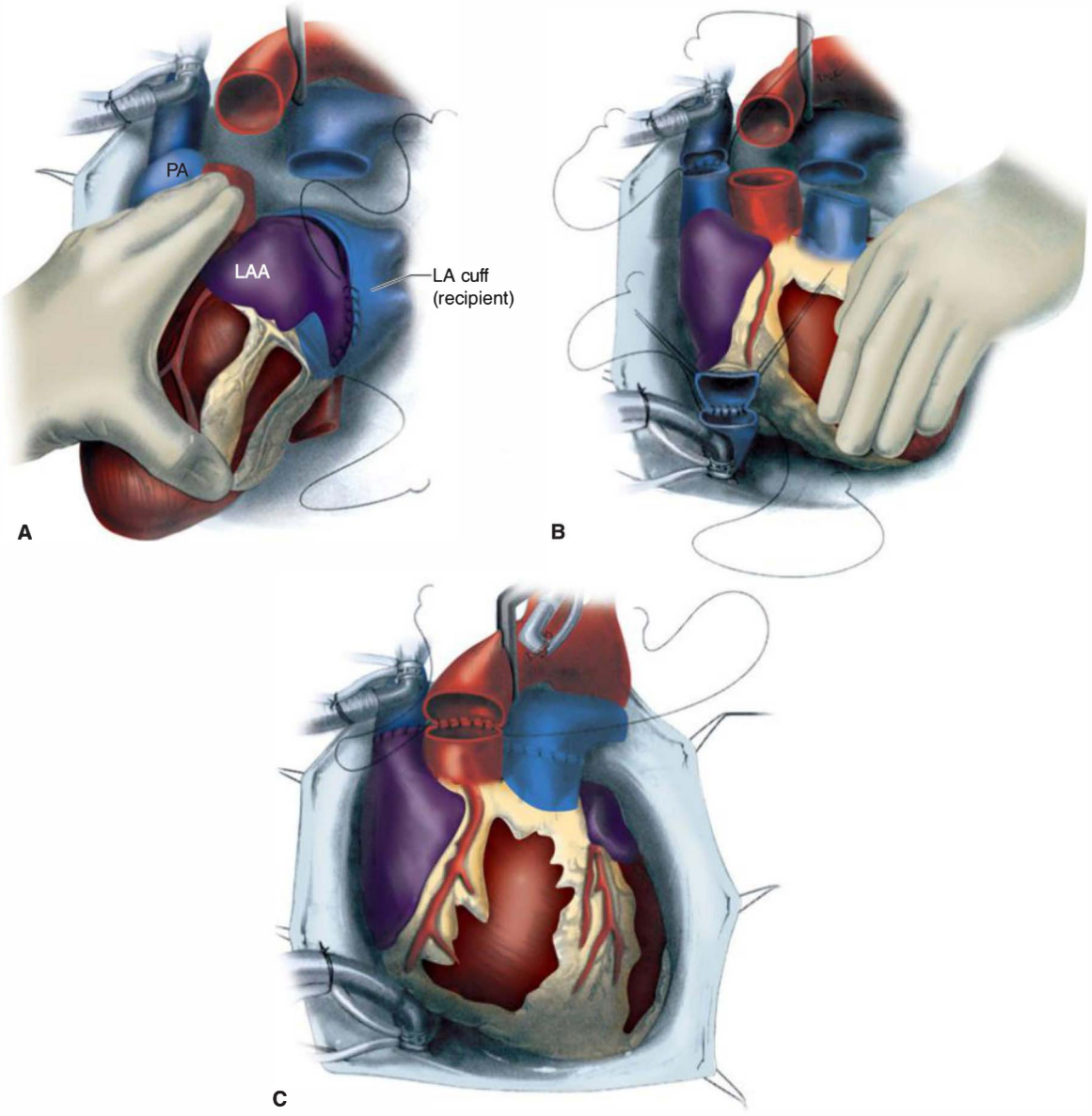



**FIGURE 50-4** Performing the caval and great vessel anastomoses. (Reproduced with permission from John R, Liao K. Orthotopic heart transplantation. *Oper Tech Thorac Cardiovasc Surg* Summer 2012;15:(2):138–146. Copyright Elsevier. Fig. 4.)

period. Typically, isoproterenol is infused at a dose of 0.01 to 0.03 μg/kg/min. The goal heart rate is set to over 90 beats/min. If the heart rate fails to respond to the isoproterenol drip, epicardial pacing (preferably atrial pacing), is initiated at 90 beats/min. The bradycardia typically resolves spontaneously within 48 h postoperatively with weaning of the isoproterenol drip. Besides its chronotropic effect, isoproterenol often improves cardiac output by reducing pulmonary vascular resistance. Cardiac output and $Svo_2$ should be closely monitored during the weaning of isoproterenol because both parameters can drop despite maintenance of an adequate intrinsic heart rate. Terbutaline may be required to keep the heart rate over 60 beats/min once the patient resumes oral intake. Occasionally, a permanent pacemaker may be necessary if the heart rate remains less than 60 over a sustained period of time.[24]

A second β-adrenergic agent such as epinephrine is added in the early postoperative period if the patient's cardiac output is inadequate or if isoproterenol leads to excessive tachycardia or significant arrhythmias. If the patient's systemic blood pressure and peripheral vascular resistance are low, a vasoactive agent such as vasopressin is added. Vasopressin is

preferred over other vasoconstrictors due to its limited effect on pulmonary vascular resistance. A milrinone infusion is initiated in the setting of significant pulmonary hypertension or right heart failure.

Low cardiac output early after transplantation can be multifactorial. The increased use of older marginal donor hearts, prolonged donor heart ischemic time, and mismatch of donor and recipient weight all contribute to early graft dysfunction. The treatment algorithm for low cardiac output is similar to that used in routine cardiac surgery patients. Maintaining an adequate heart rate with an isoproterenol infusion or atrial pacing is crucial to optimizing early cardiac allograft function, followed by maintaining adequate preload by maintaining central venous pressures between 10 and 18 mm Hg. One or more β-adrenergic inotropic agents are usually required in the early postoperative period. Milrinone is useful in the setting of significant pulmonary hypertension and/or right ventricular dysfunction. If low cardiac output persists despite these interventions, an echocardiogram should be obtained to rule out cardiac tamponade and assess left and right ventricular function.

Early graft failure is unusual but often results from poor myocardial protection or early acute allograft rejection. Early endomyocardial biopsy to detect cellular rejection or immunofluorescence staining to identify humoral rejection may be required. True hyperacute cardiac rejection is extremely rare in the modern era of transplantation. Progressive left ventricular dysfunction due to primary graft failure may require further support with an intra-aortic balloon pump. A left or biventricular assist device may be required if multiorgan failure and severe acidosis cannot be reversed by medical management. Short-term extracorporeal ventricular assist devices can be used to support the failed heart for up to 2 weeks to allow the myocardium to recover from ischemia or to allow antirejection treatment to work. Ventricular assist devices are inserted in a standard fashion, with the inflow cannula inserted in the appropriate atrium and outflow cannula inserted into the appropriate great vessel.[25]

Recipients with a preoperative pulmonary vascular resistance above 3 Wood units are at an increased risk of developing elevated pulmonary vascular resistance in the early postoperative period, resulting in acute right heart failure. Several measures can be taken to prevent right heart failure, including using a slightly "oversized" donor and/or using a graft from a male donor to a female recipient. Donor graft ischemic time must be minimized. Excessive blood and blood product transfusions can be avoided by giving activated factor VII to correct significant coagulopathy. Hypoxia and hypercapnia should be corrected. Early initiation of milrinone and inhaled nitric oxide can be used for their pulmonary vasodilatory effects. Finally, leaving the chest open can be helpful in avoiding mechanical compression of an edematous, struggling right ventricle.[26] Inserting a right ventricular assist device in the setting of a high PVR is of limited utility with generally poor clinical outcomes.

## Immunosuppressive Management

Systemic immunosuppressive therapies are used to prevent or treat cardiac allograft rejection while minimizing both drug toxicities and the major sequelae of immunosuppression, namely infection and malignancy. Most immunosuppressive regimens consist of "triple-therapy" immunosuppression: corticosteroids, calcineurin inhibitors, and antiproliferative agents.[27,28]

Corticosteroids are nonspecific anti-inflammatory agents, generally effecting significant lymphocytic depletion. They reversibly block T cell and antigen-presenting cell-derived cytokine and cytokine-receptor expression that otherwise would occur as a consequence of T-cell activation. The nonspecific action of steroids leads to many side effects such as: weight gain, glucose intolerance, gastric distress, hyperlipidemia, and hypertension.

Calcineurin inhibitors, namely cyclosporine, a small fungal cyclic peptide, and tacrolimus-FK506 (Prograf), a macrolid antibiotic, have become the cornerstone of immunosuppressive therapy in solid organ transplantation. Cyclosporine binds to a group of immunophilins called cyclophilins, which are important biologic molecules present in all tissues. Tacrolimus forms a complex with FK506 binding proteins (FKBP). These complexes bind to calcineurin, a pivotal enzyme in T-cell IL-2 production, thereby inhibiting cytokine transcription by CD4 cells. Blockade of cytokine production and cytokine-receptor expression inhibits T-cell proliferation and differentiation so that the various effector arms of the immune response are not activated. Compared to cyclosporine, Prograf causes less nephrotoxicity.[29]

The antiproliferative agent, mycophenolate mofetil (MMF, CellCept), is a selective inhibitor of the de novo pathway of purine biosynthesis, thereby providing more specific and potent inhibition of T- and B-cell proliferation. MMF causes less bone-marrow suppression compared with the other agents in its class.

Daclizumab (Zenapax) is a monoclonal antibody that is an IL-2 receptor antagonist, which is typically useful in the setting of renal insufficiency or in recipients suffering from gastrointestinal dysfunction for an extended period of time.

## Immunosuppressant Dosing

Methylprednisolone is typically administered to the cardiac transplant recipient preoperatively (1000 mg IV) and upon reperfusion of the donor heart (500 mg IV). Additional methylprednisolone (125 mg IV) is dosed every 8 h for three doses after the patient has returned to the intensive care unit. Prednisone is initiated at 1 mg/kg/day in two divided doses and progressively tapered over a 4-week period by 5 mg/day to 20 mg twice a day (Table 50-6). Patients must be free of rejection for 3 months before steroids are completely withdrawn.

Prograf is typically started within the first three postoperative days if the patient's renal function is normal. The

**TABLE 50-6: Typical Prednisone Taper Regimen**

| | |
|---|---|
| Month 1 | Prednisone 0.3 mg/kg/d |
| Month 2 | Prednisone 0.2 mg/kg/d |
| Month 3 | Prednisone 0.1 mg/kg/d |
| Month 4 | Prednisone 0.05 mg/kg/d or 2.5 mg/d |
| Month 5 | Prednisone discontinued |

starting dose of Prograf is 0.5 mg twice a day and is increased to 2 mg twice a day depending on the serum drug levels. The patient's renal function or creatinine is closely monitored during Prograf dosing. The 12-h trough level of Prograf is maintained between 10 and 15 mg/L immediately after transplant, and tapered afterward (Table 50-7).

Mycophenolate mofetil (1500 mg PO) is given preoperatively and continued postoperatively (2–3 g IV/PO per day in two divided doses). Serum levels of MMF are maintained at 2 to 4 mcg/ml and the dose is further titrated to keep the white blood cell count above 4000/dL.

## Treatment of Cardiac Allograft Rejection

Rejection of the transplanted heart is a major cause of morbidity and mortality in the first year after heart transplantation. Rejection is classified as hyperacute, acute cellular, acute humoral (antibody-mediated), or chronic (allograft vasculopathy).[30]

*Hyperacute rejection* occurs within minutes to hours of allograft reperfusion and is caused by preformed antibodies to ABO blood group antigens, HLA, or endothelial antigens. With ABO matching of recipients to donors and prospective and/or virtual crossmatching of patients who have been previously sensitized to HLA, hyperacute rejection is rare. When it does occur, it is catastrophic because preformed antibodies bind to endothelial antigens on the transplanted heart, resulting in complement-mediated coronary thrombosis and marked cardiac allograft dysfunction.

*Acute cellular rejection* may occur at any time after transplantation but occurs most commonly in the first 3 to 6 months. It is a T cell–mediated response with myocardial infiltration by lymphocytes and macrophages with resultant myocytolysis. The diagnosis is made by endomyocardial biopsy with a standardized grading scheme ranging from mild to moderate to severe acute rejection.[31] Moderate rejection by endomyocardial biopsy is associated with mononuclear cell infiltrates and myocytolysis and generally prompts antirejection therapy that varies according to the histological severity (i.e., grade of rejection) and graft performance. Patients with acute cellular rejection may display no signs or symptoms, but often notice mild fatigue or dyspnea. Signs of right ventricular dysfunction are often consistent with elevated jugular venous pressures. More severe rejection may be associated with signs of left ventricular dysfunction. Therapy may include intravenous or oral steroids, monoclonal or polyclonal antilymphocyte agents, or an increase or change in existing immunosuppressant dosing.

Routine endomyocardial biopsy remains the gold standard for monitoring and grading of cardiac allograft rejection. The first consensus statement on grading rejection based on endomyocardial biopsy specimens was published in 1990. It described the various histologic patterns of inflammation in biopsy specimens and is summarized in Table 50-8.

*Antibody-mediated rejection (AMR)* refers to allograft injury resulting from activation of the complement system, typically by recipient-generated antibodies directed against the allograft tissue antigens. Although AMR most commonly occurs months to years following transplantation, a rare subtype, hyperacute rejection, can occur within minutes to hours after transplantation. Risk factors for developing AMR include history of multiple pregnancies, previous transplantation, blood transfusions, sensitization by OKT3 induction therapy, and use of ventricular assist devices.[32,33]

Diagnosing AMR can be difficult. The criteria for the diagnosis of AMR include complement deposition in capillaries (especially CD4), capillary endothelial swelling, and inflammation involving the capillaries, most typically macrophage infiltrates located in the vessel wall and lumen. A consensus statement on diagnosing AMR was established by the ISHLT in 2004; AMR 0 is reported for those cases that provide no evidence of AMR, whereas AMR 1 is used to denote a diagnosis of AMR.[34]

Endomyocardial biopsy is generally performed weekly for the first postoperative month, after which biopsies are

**TABLE 50-7: Typical Prograf Blood Level Taper Schedule**

| | |
|---|---|
| 0–3 months | 10–15 mg/L |
| 3–6 months | 8–12 mg/L |
| 6–9 months | 6–12 mg/L |
| 9–12 months | 6–12 mg/L |
| After year 1 | 6–10 mg/L |
| Off prednisone | 6–10 mg/L |

**TABLE 50-8: International Society for Heart Lung Transplantation (ISHLT) 1990 Classification of Acute Cellular Rejection in Transplant Endomyocardial Biopsy Specimens**

Grade 1A: Focal, mild acute rejection
Grade 1B: Diffuse, mild acute rejection
Grade 2: Focal, moderate acute rejection
Grade 3A: Multifocal, moderate rejection
Grade 3B: Diffuse, borderline severe acute rejection
Grade 4: Severe acute rejection

obtained at less frequent intervals. The clinical manifestations of cardiac transplant rejection are variable and may or may not correlate with the histologic severity of rejection. During an episode of rejection, the clinical presentation can range from no symptoms to profound heart failure. Arrhythmias and sudden death resulting from rejection have also been reported following heart transplantation. Ischemia may be produced secondary to cardiac allograft vasculopathy (Typical angina is usually absent owing to the fact that the donor heart is denervated.

Patients presenting with at least grade 3A rejection are treated with pulse steroids in the form of prednisone 1000 mg/day for three consecutive days. If such rejection is encountered within the first postoperative month or during the initial hospitalization, three doses of intravenous methylprednisolone (10 mg/kg/day) are administered. Dosing of other maintenance immunosuppression agents are adjusted to obtain optimal levels. Patients with any positive grade of biopsy and hemodynamic compromise are admitted to the hospital and receive intravenous thymoglobulin, a polyclonal antibody. If biopsy specimens of hemodynamically compromised patients show no evidence of cellular rejection, immunofluorescence studies should be performed and may confirm humoral-mediated rejection. Plasmapheresis is initiated if humoral rejection is strongly suspected or confirmed. Occasionally, empiric antirejection therapy may be started for hemodynamically compromised patients without a definitive biopsy result or diagnosis. If the patient has had a positive donor-specific crossmatch or has clinic signs of early acute rejection, early immunosuppression is directed toward decreasing the humoral antibody load and B-lymphocyte proliferation. Plasmapheresis may also be performed to rapidly decrease antibody load.[35]

## Complications of Immunosuppressive Therapy

Each immunosuppressive agent carries a host of side effects. Steroids are known to cause Cushingoid features, osteoporosis, peptic ulcer disease, and glucose intolerance. Reduction and elimination of steroids is the most effective means to ameliorate these side effects. Occasionally, oral hypoglycemic medications and even insulin are used to treat hyperglycemia resulting from steroid use. Important side effects of cyclosporine include renal dysfunction and hypertension. Careful monitoring of serum cyclosporine levels with an eye towards achieving the lowest effective levels helps mitigate these side effects.

### INFECTION

Despite improved immunosuppressive therapies, infection remains a serious complication in cardiac transplant recipients. In the immediate postoperative period, the most common infection is ventilator-associated pneumonia resulting from prolonged intubation. Early extubation and aggressive pulmonary toilet measures are critical to preventing hospital acquired pneumonia. Pneumonia is treated with broad-spectrum antibiotics with antibiotic sensitivities closely followed.

Despite the prophylactic use of trimethoprim–sulfamethoxazole, CMV infections are still a major source of morbidity after transplantation. Patients with CMV-negative serologies who receive hearts from CMV-positive donors are at an increased risk for developing serious CMV infections. Valganciclovir has replaced ganciclovir and is currently recommended for CMV prophylaxis if the donor and/or recipient have positive CMV serologies. If both the recipient and donor have negative CMV serologies, valganciclovir prophylaxis is generally not indicated. The dosing of valganciclovir is based on the patient's renal function, with 900 mg/day being a typical dose in patients with normal renal function and 450 mg/day for patients with mild-to-moderate renal impairment.

### MALIGNANCY

The risk of malignancy in solid organ transplant recipients is elevated compared with the general population. This is believed to be a result of long-term immunosuppression compromising the ability of the patient's immune system to reverse precancerous tissue changes and incipient malignancy. According to the registry of the International Society for Heart and Lung Transplantation (ISHLT) in 2008, the cumulative prevalence of malignancy in heart transplantation recipients is 2.9, 15.1, and 31.9 percent at 1, 5, and 10 years, respectively.[36]

Skin cancer is the most common malignancy in heart transplant recipients, with an incidence of 1 percent at 1-year posttransplant, 10 percent at 5 years, 20 percent at 10 years, and 29 percent at 14 years. When treated early, most forms of skin cancer do not result in death. Lymphoproliferative malignancies are much less frequent than skin cancer. The incidence of lymphoproliferative malignancies is 1, 2, 4, and 5 percent at 1, 5, 10, and 14 years, respectively, after transplantation, and are much more difficult to cure. The most common solid organ malignancies in heart transplant patients are prostate, lung, and breast cancers. The incidences of these malignancies are similar to those in the general population. The principles of treating malignancies in heart transplant patients are the same as for the general population. Attenuation of immunosuppressive regimens in afflicted patients is useful for controlling tumor progression.

### CARDIAC ALLOGRAFT VASCULOPATHY

CAV, also known as accelerated graft arteriosclerosis, generally refers to concentric luminal narrowing of the epicardial and intramural coronary arteries. This process generally occurs months to years following transplantation and is currently the limiting factor in long-term cardiac allograft survival. More than one-half of adult heart transplant recipients exhibit angiographically detectable

CAV by 10 years posttransplantation. In the 2009 ISHLT Registry report on data from more than 84,000 heart transplant recipients, the overall prevalence of CAV in survivors at 1, 5, and 10 years after transplantation was 8, 30, and 51 percent, respectively. Early CAV, diagnosed within the first year after transplantation, is a powerful predictor of 5-year mortality. Compared to conventional coronary angiography, intravascular ultrasound (IVUS) can detect coronary intimal thickening at a much earlier stage. Some studies show that first-year IVUS data can provide an early marker for long-term outcomes. The most important predictors for the development of CAV were found to be older donors, donor history of hypertension, younger recipients, number of HLA–DR mismatches, and recipient pretransplant diagnosis of ischemic heart disease. A variety of immune and nonimmunologic factors contribute to the pathogenesis of CAV. It is believed that CAV arises with ischemic injury to the donated organ's endothelial cells. In response, both immunologic and nonimmunologic factors act on the endothelium, initiating a cascade of immunologic responses. Eventually, upregulation of complement, inflammatory mediators, and cytokines leads to the progression of CAV. Immunosuppressive medications, such as cyclosporine and corticosteroids, are now thought to contribute to endothelial cell injury and ultimately to the intimal hyperplasia characteristic of CAV.[37]

Current medical therapies are not effective and can only slow the progression of CAV. Proliferation inhibitors (e.g., sirolimus and everolimus), and statin drugs have demonstrated some benefit in preventing CAV. Primary strategies for managing CAV include modification of cardiovascular risk factors, including control of hypertension and diabetes, smoking cessation, weight loss, surgical and percutaneous revascularization, and retransplantation. For patients with severe CAV, revascularization with drug-eluting stents or coronary bypass grafting is considered palliative therapy, with retransplantation offering a more definitive solution.

## CLINICAL OUTCOMES

The median survival after cardiac transplantation is currently 10 years for the entire cohort of adult and pediatric recipients, with a median survival of 13 years for those surviving to 1 year. Median survival rates have steadily improved from 8.3 years during the 1980s to 10.4 years during the 1990s—and survival has further improved since 2000. The mortality risk is highest in the first 6 months after transplant; the improvement in survival most recently has been attributed to lower mortality during this early posttransplant period. Past 1 year after transplant, the mortality rate is fairly constant, approximately 3 to 4 percent/year, which is higher than the mortality rate of the general population. In the last 20 years, long-term survival of those patients who are alive at 1 year has not significantly improved, and it is likely that the potential for further survival improvement now lies in approaches that reduce long-term mortality rates.

Graft failure is the leading cause of death in the first 30 days after transplant (39 percent of deaths) and continues to remain prominent throughout the early posttransplant period. Within the first 30 postoperative days, most cases are due to primary graft failure. Subsequent to this period, graft failure is more likely due to chronic graft injury from AMR or CAV. Acute rejection is now a fairly uncommon cause of mortality, responsible for no more than 11 percent of deaths.

Deaths related to CAV become prominent between 1 and 3 years after transplantation and are responsible for 10 to 15 percent of deaths thereafter. The rate of death from malignancy also increases in this period and is responsible for approximately 20 percent of deaths 3 or more years after transplant. The risk of death due to infection is highest in the first year after transplant, comprising 29 percent of deaths between 2 and 12 months posttransplant, after which the risk decreases to about 10 percent. Renal failure as the primary cause of death increases steadily after transplant.

Within the first year after cardiac transplantation, patients bridged to heart transplantation with mechanical circulatory support devices appear to have a higher risk of death compared with recipients not requiring mechanical circulatory support. Patients with congenital heart disease carry a higher mortality risk, and patients with ischemic cardiomyopathy fare somewhat worse than those with nonischemic cardiomyopathy. Comorbidities that are significant risk factors for recipient mortality include the need for hemodialysis, mechanical ventilation, blood transfusion, and recent infection. Recipient and donor age, allograft ischemic time, and serum markers of hepatic and renal dysfunction also affect recipient survival.

Mortality rates at 5 years posttransplant are affected to a large degree by factors similar to those affecting 1-year mortality. Additional risk factors at this point include past pregnancy, female allograft allocation to a male recipient, and prior stroke. The risk factors that affect 10-year mortality rates are similar to those that affect 1- and 5-year mortality rates. The additional significant predictor of risk at 10 years after transplant is gender—female recipients and male recipients receiving female allografts appear to have a higher risk of death than males receiving male allografts. A PRA level of more than 10 percent is also a significant mortality risk factor, although the increased risk is modest.

Only a few factors are associated with 20-year mortality rates. Younger recipient age at transplant favor 20-year survival. Donor age and allograft ischemic time, consistent predictors of mortality at 1, 5, 10, and 15 years after transplant, are not associated with mortality at 20 years. A possible explanation for this is that during the 1980s, heart allografts from older donors were not routinely used and longer allograft ischemic times were avoided. Recipients who underwent transplant for nonischemic cardiomyopathy fared better than those with ischemic cardiomyopathy, and patients with congenital heart disease fared better than those who underwent transplant for nonischemic cardiomyopathy.

## FUTURE DIRECTIONS

The last four decades have witnessed steady improvement in outcomes among cardiac transplant recipients. This improvement has been attributed to better management of heart failure patients on the waiting list, introduction of new immunosuppressants, the increasing use of LVADs as bridge support, and improved donor organ preservation. However, many obstacles remain. Limited donor organ availability has remained constant for decades. The potential solutions for donor organ shortage reside in expanding the pools of alternative donors for alternative recipients who are excluded by conventional criteria and increasing efforts in xenotransplantation research, which could potentially solve the donor shortage. A portable organ perfusion device to continuously perfuse the donor heart to extend the current preservation time limit of 6 h will improve organ availability and provide opportunities for better matching. Advances in small, durable, and implantable ventricular assist devices as destination therapy will ease the increasing demand for donor hearts and ultimately delay or obviate heart transplantation in many end-stage heart failure patients.

Mortality from infection, malignancy, and renal failure can be attributed to overly aggressive immunosuppressive therapies. Deaths from rejection, CAV, and late graft failure often result from inadequate immunosuppression. Consequently, there is a need to assess the individual transplant recipient's immune status and risks more accurately and tailor immunosuppressive therapies accordingly. Immune surveillance with noninvasive techniques may lead to earlier detection of rejection and more efficient treatment. Finally, the continued development of new and improved immunosuppressants will undoubtedly reduce the side effects currently associated with immunosuppressive regimens.

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## CARDIAC TRANSPLANTATION BOARD REVIEW QUESTIONS (CHAPTER 50)

1. Which of the following is a contraindication to cardiac transplantation?
   A. Recipient PVR is greater than 5 Wood units.
   B. Recipient had breast cancer 5 years ago.
   C. Recipient was transfused 2 months ago.
   D. Recipient had an LVAD placed 2 months ago.
   E. Recipient has a creatinine of 2.0.

2. Which of the following situations carries the highest potential operative mortality?
   A. A younger recipient receives a younger donor heart with a short ischemic time.
   B. A younger recipient receives an older donor heart with a long ischemic time.
   C. An older recipient receives a younger donor heart with a long ischemic time.
   D. An older recipient receives a younger donor heart with a short ischemic time.
   E. An older recipient receives an older donor heart with a long ischemic time.

3. What is the appropriate strategy prior to transplantation in a potential recipient who has received a recent blood transfusion?
   A. Perform a prospective crossmatch.
   B. Perform a virtual crossmatch.
   C. Wait 2 weeks, perform PRA, and then list for a crossmatch.
   D. Accept an appropriate donor and wait for the retrospective crossmatch.
   E. Pretreat with thymoglobulin and adjust postoperative immunosuppression according to the retrospective crossmatch.

4. What part of the donor heart is at greatest risk for compromise during procurement?
   A. Donor left atrium on the right side
   B. Donor left atrium on the left side
   C. Donor right atrium near the SVC
   D. Donor right atrium near the IVC
   E. Donor pulmonary artery

5. At 5 years after cardiac transplantation, what percentage of recipients will have CAV?
   A. 10 percent
   B. 20 percent
   C. 30 percent
   D. 40 percent
   E. 50 percent

## ANSWERS

1. **Answer: A.** The recipient PVR should ideally be less than 5 Wood units. Patients that are cancer-free after 5 years are considered acceptable for transplantation. Transfusion within 2 months mandates a PRA prior to transplantation. A patient with placement of an LVAD 2 months ago would be approaching adequate time for transplant listing. Elevated creatinine is not a contraindication to transplantation but warrants adjustment of antirejection therapies.
2. **Answer: E.** The combination of an older recipient with possible comorbidities and an older donor heart that is less resilient to an extended period of ischemia is associated with the highest potential operative mortality. In general, young donor organs will do well, even with extended ischemic times. An older donor heart should not be used in a younger recipient unless there is no alternative.
3. **Answer: A.** Although a prospective crossmatch will limit the number of potential donors, this is the safest approach. A virtual crossmatch still needs a current PRA and a 2-week waiting period from the last transfusion. After waiting 2 weeks, a crossmatch may not be necessary. Accepting an appropriate donor based only on a retrospective crossmatch carries an undue risk of AMR. Pretreatment with thymogloblin will not eliminate all risk of AMR.
4. **Answer: B.** The confluence of the left pulmonary veins can be quite short and difficult to appreciate during the procurement, particularly when leaving a cuff of left atrium for concomitant left lung procurement.
5. **Answer: C.** Approximately 30 percent of recipients will have evidence of CAV 5 years after transplantation.

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# 51 Mechanical Circulatory Support

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## INTRODUCTION

The history of mechanical circulatory support (MCS) parallels that of cardiac surgery and began with the introduction of the Gibbon bubble oxygenator.[1] That revolutionary device opened up the field of cardiac surgery and was one of the major medical advances of the last century. Soon after the use of cardiopulmonary bypass (CPB) became commonplace, failure to wean from CPB became recognized as a problem whose solution required temporary cardiac support to enable postcardiotomy cardiac recovery. Spencer and coworkers utilized postoperative femoral CPB in 3 patients, one of whom survived and ushered in the modern era of temporary MCS.[2] This was soon followed by the use of the first extracorporeal mechanical assist device by DeBakey et al. in 1964 and the subsequent development of the intraaortic balloon counterpulsation device, variations of which are still in use today. Kantrovitz, Cooley, Oyer, Devries, and others were responsible for other notable firsts including the first successful bridge to transplant (BTT) and first successful total artificial heart (TAH) implant.[3-7] Notable clinical landmarks in the history of MCS are shown in Table 51-1. In this chapter, we review the major indications for MCS as well as the various options available.

## INDICATIONS FOR MECHANICAL CIRCULATORY SUPPORT

Generally speaking, there are three primary indications for the use of MCS: "bridge to recovery" (BTR), "bridge to transplant" (BTT), and "destination therapy" (DT). Data on MCS devices implanted in the United States are kept by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS).[8] According to the second INTERMACS annual report that provides information on FDA-approved device implantations from 2006 to 2009, the most common indication for MCS was BTT (45.4 percent), followed by DT (9.2 percent), and BTR (2.3 percent) (Fig. 51-1). Bridge to candidacy for transplantation, or "bridge to decision" is a fourth category that has emerged and includes patients whose candidacy for transplantation has not been decided for medical or social reasons. This accounted for 41.9 percent of all device implantations during this time period. Within each of these categories, specific device therapy can be broken down into short-term (days to weeks) and long-term (weeks or longer) therapy.

BTR is used in patients who have severe, acutely decompensated heart failure from potentially reversible causes who may eventually recover myocardial function but whose native heart is unable to provide sufficient end organ perfusion without assistance. This therapy serves to unload the damaged heart to allow remodeling and recovery while providing improved tissue perfusion to vital organs. Indications for BTR therapy include postcardiotomy support following cardiac surgery, acute viral cardiomyopathic syndromes, hemodynamic instability, and myocardial infarction. For BTR, short-term devices are typically used as their cost is lower and implantation is easier. In certain patients in extremis and in whom neurologic status and candidacy for cardiac transplantation or longer term mechanical assist therapy is unknown, a short-term device can potentially serve as a bridge to a long-term device in a "bridge to a bridge" scenario in which the short-term device is replaced by a long-term device for DT or BTT prior to cardiac transplantation. BTR has also been used in patients with chronic advanced CHF with the hope that a period of unloading will enable ventricular remodeling and recovery, allowing device removal.

BTT is currently the most common indication for MCS today. The intent of device therapy for this group of patients is not only to provide temporary support for a failing heart but also to improve end organ function, making the potential recipient healthier prior to transplantation. Studies have demonstrated improved survival to transplantation and improved posttransplant survival compared with inotrope supported patients.[9]

DT is the phrase coined to describe the use of left ventricular assist devices (LVADs) as a final therapy to support patients until their death. These patients are those

**TABLE 51-1: Clinical Milestones in the Development of Mechanical Circulatory Assistance**

| Year | Investigator | Type of Device | Comments |
|---|---|---|---|
| 1953[1] | Gibbon | Heart–lung machine | Closure of ASD in human |
| 1959[2] | Spencer | Femoral bypass | First case of successful recovery postcardiotomy |
| 1963[3] | DeBakey | Pneumatic paracorporeal VAD | Postcardiotomy failure; 4 days survival |
| 1968[4] | Kantrovitz | IABP | Clinical application of IABP |
| 1969[5] | Cooley | Liotta TAH | Successful bridge to transplant but patient died posttransplant |
| 1984[6] | Oyer | Novacor | Successful bridge to transplant, patient survived |
| 1980[7] | DeVries | JarvikTAH | First human implant |

IABP, intraaortic balloon pump; TAH, total artificial heart; VAD, ventricular assist device.

without expected recovery of myocardial function, but who are not candidates for cardiac transplantation due to older age, obesity, smoking, cancer, pulmonary hypertension, social concerns, or other advanced organ dysfunction. Longer term support devices intended for extended treatment periods are utilized for this purpose, and this is currently the second most common indication for device implantation today.

**Device strategy at time of implant of primary LVAD (INTERMACS: June 2006–March 2009)**

| Pre-implant device strategy | No. (*N* = 1092) | % |
|---|---|---|
| Bridge to transplant (currently listed) | 496 | 45.4 |
| Bridge to candidacy | 458 | 41.9 |
| Listing likely | 305 | 27.9 |
| Listing moderately likely | 100 | 9.2 |
| Listing unlikely | 53 | 4.9 |
| Planned DT (permanent device) | 100 | 9.2 |
| Bridge to recovery | 25 | 2.3 |
| Rescue therapy | 10 | 0.9 |
| Other | 3 | 0.3 |
| Total | 1092 | 100.0 |

DT, destination therapy; INTERMACS, Interagency registry for mechanical circulatory support; LVAD, left ventricular assist device.

**FIGURE 51-1** LVAD implantation in the United States 2006 to 2009 by indication. (Adapted from Kirklin JK, Naftel DC, Kormos RL, et al. Second INTERMACS annual report: More than 1000 primary left ventricular assist device implants. *J Heart Lung Transplant* 2010;29:1–10.)

## SPECIFIC DEVICES

MCS devices can be classified by their mechanism of action (Table 51-2). These include the first-generation pulsatile devices, the second-generation continuous axial flow devices,

**TABLE 51-2: Types of Assist Devices Classified by Mechanisms**

- Extracorporeal support
  - Centrifugal pumps (radial flow/rotodynamic)
    - Sarns 3M
    - St. Jude
    - Nikkiso
    - Medtronic Biopump
  - Newer centrifugal pumps
    - HeartQuest System
    - VentrAssist
    - HeartMate III
    - Terumo Dura Heart
    - Kriton VAD
    - CentriMag
- Paracorporeal support
  - ABIOMED BVS 5000
  - ThoratecpVAD
  - Berlin Heart EXCOR
  - Tandem Heart
- Intracorporeal support
  - Aortic compression/counterpulsation
    - IABP
    - Kantrovitz CardioVad Systems
    - AbiomedImpella
  - Ventricular assist devices
    - ThorateciVAD
    - HeartMate XVE LVAD
    - HeartMate II LVAD
    - Novacor LVAD
    - Heart Saver VAD
    - Arrow LionHeart LVAD (Penn State LVAS)
  - Total artificial heart (TAH)
    - Liotta TAH
    - Jarvik 7 TAH
    - Aktsu III TAH
    - AbioCor TAH
    - Syncardia TAH
    - Penn State/3M TAH (ABIOMED Inc., acquired from BeneCor)
- Axial flow pumps
  - Jarvik 2000
  - HeartMate II
  - MicroMed-DeBakey VAD
  - Pittsburgh Streamliner mixed flow pump
  - CorAid LVAS (Arrow Inc.)
  - Berlin Heart INCOR
- Epicardial compression devices
  - Anastedt cup
  - CardioSupport Systems
  - Heart Booster (ABIOMED)
  - CorCap (Acorn)
  - Myosplint (Myocor)
  - Skeletal Muscle Systems
- Extracorporeal membrane oxygenation (ECMO)

**TABLE 51-3: Mechanical Assist Devices Used in the United States**

| Device | FDA-Approved | Ventricle Supported | Duration of Support | Home Discharge |
|---|---|---|---|---|
| ABIOMED BVS 5000 | 1992 | L, R, B | S | No |
| Novacor | 1993 | L | LG | Yes |
| HeartMate IP | 1994 | L | LG | No |
| ThoratecpVAD | 1996 | L, R, B | S, LG | Yes |
| HeartMate VE | 1996 | L | LG | Yes |
| HeartMate XVE | 2002 | L | LG | Yes |
| ABIOMED AB5000 | 2003 | L, R, B | S | No |
| ThorateciVAD | 2004 | L, R, B | S, LG | Yes |
| Syncardia TAH | 2004 | B | S, LG | No |
| HeartMate II | 2008 | L | LG | Yes |
| | **Year Trial Began** | | | |
| LionHeart | 2001 | L | LG | Yes |
| Jarvik 2000 | 2002 | L | LG | Yes |
| Micromed DeBakey | 2002 | L | LG | Yes |
| AbioCor | 2002 | B | S, LG | Yes |
| VentrAssist | 2003 | L | LG | Yes |
| TandemHeart | 2006 | L | LG | Yes |
| ABIOMED Impella | 2006 | L | S | Yes |
| EXCOR | 2007 | L | LG | Yes |
| DuraHeart | 2008 | L | LG | Yes |
| Heartware | 2008 | L | LG | Yes |
| INCOR | 2010 | L | LG | Yes |
| EVAHEART | 2010 | L | LG | Yes |
| Levacor | 2010 | L | LG | Yes |

L, left ventricular support; R, right ventricular support; B, biventricular support; S, short-term support; LG, long-term support.

the third-generation centrifugal pumps, and TAHs.[10] Some FDA-approved devices are listed in Table 51-3.

## Early Devices

Early devices for MCS were easy to insert, relatively inexpensive, and the most easily available of the assist devices. They have been designed for short-term support lasting hours to days, and are most often employed for postcardiotomy failure.

### NONPULSATILE, CENTRIFUGAL/ROTODYNAMIC RADIAL FLOW PUMPS

Blood flow for these devices is generated by rotating blades or impellers.[11] These devices do not have valves or multiple moving or occluding parts (Fig. 51-2), theoretically reducing the potential for hemolysis. These devices require priming with volumes differing from pump to pump (52–87 mL).



**FIGURE 51-2** BioMedicus (Medtronic Inc.) Centrifugal pump. (Copyright 2010 Medtronic, Inc.)

Devices of this class are capable of providing high flow rates with low rises in pressure. Several commercial devices are available, including the Carmeda Bio-Pump and the BIO-PUMP (Medtronic Inc, Minneapolis, MN), the Sarns pump (Terumo Cardiovascular Systems Ann Arbor, MI), and the Nikkiso pump (Nikkiso Pumps America Inc., Plumsteadville, PA). These devices are not designed for long-term use. Indications include left heart bypass for thoracic aortic surgery, postcardiotomy ventricular failure, extracorporeal membrane oxygenation (ECMO), and bridge to transplantation or to another VAD. Cannulation sites commonly used for left heart bypass include the left superior pulmonary vein or left atrium (inflow) and the ascending aorta or femoral artery (outflow). For right heart bypass, inflow is obtained via right atrial cannulation with outflow directed into the pulmonary artery. Cannula fixation is important with these and other devices, since most hemorrhagic complications are due to cannula dislodgement. Anticoagulation is required after device insertion and must be monitored closely.

There are no firm criteria for device weaning and removal, but the achievement of hemodynamic stability and a documented cardiac recovery dictate the removal strategy. Typically a gradual reduction in support is initiated over hours to days with device removal once minimal support is required. When a device of this class fails, it is often due to breakdown of the pump head seal, leading to the entry of fluid into the magnetic chamber.[12] Clinical experience has shown that these pumps are especially well suited for left heart bypass and for short-term postcardiotomy left ventricular failure. In one study, 62 patients were supported using the centrifugal pump for postcardiotomy failure; 22 patients required left ventricular support, 9 required right ventricular

support, and 31 required biventricular support. Support was extended for up to 19 days, with 42 patients weaned successfully, 27 patients discharged home, and 18 patients surviving more than 1 year.[13] Other studies have reported similar results for short-term support.[14,15]

## PARACORPOREAL PULSATILE DEVICES

***Abiomed BVS 5000.*** This device was approved by the FDA in 1992 for use in all types of recoverable heart failure. It is an external pulsatile VAD capable of supporting the right and/or left ventricles for days to weeks. This device is a pneumatically driven, asynchronous, pulsatile, automated, self-regulating, polycarbonate-housed dual-chamber pump system (Fig. 51-3). The atrial chamber of this two-chamber pump fills passively by gravity drainage; the volume is usually about 100 mL, and the internal chamber is made of flexible polyurethane. The atrial chamber drains into the ventricular chamber through a trileaflet valve made of proprietary material. During systole, compressed air is delivered into the ventricular chamber; it compresses the polyurethane bladder and ejects its contents toward the patient. The pumping unit and console are located outside the body; the inflow and outflow cannulas are tunneled subcutaneously into the mediastinum. Each pump is capable of delivering a maximal output of 6 L/min at a constant stroke volume of 80 mL.

The implantation technique for the BVS 5000 varies from center to center. For right ventricular support, the inflow cannula is placed into the mid-right atrium and secured firmly with pledgeted purse-string sutures. Another alternative is to insert this cannula directly into the right ventricle through its diaphragmatic surface, particularly if there are adhesions from previous surgery. The outflow cannula is anastomosed to the main pulmonary artery. For left ventricular support, the inflow cannula is placed into the left atrium via the right superior pulmonary vein, left atrial dome or directly into the left ventricle via the apex. Left ventricular apical cannulation permits complete ventricular decompression, optimizing its chance for recovery. Left ventricular apical cannulation is also advantageous if a mechanical mitral prosthesis is in place, since it permits opening and closing of the leaflets and may reduce thrombotic complications. The outflow cannula is anastomosed to the ascending aorta.

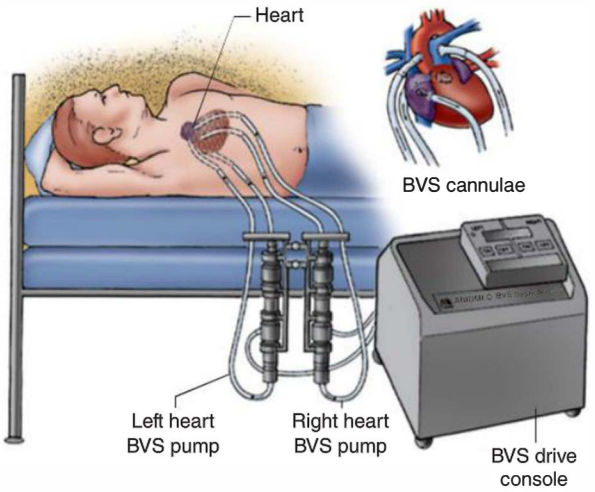



**FIGURE 51-3** Abiomed BVS 5000. (With permission from ABIOMED Inc.)

Heparin anticoagulation is required during BVS 5000 support and must be closely monitored; an activated clotting time (ACT) of 180 to 200 s is the goal. The pump is easy to manage and operated based on the principles of preload and afterload management. Limitations of this device include limited patient mobility, restricted flow capacity, and heparinization requirements.

A prospective multicenter trial evaluated the safety and efficacy of the BVS 5000 in 31 patients with hemodynamic instability despite maximal pharmacologic and IABP support. There was an improvement in mean arterial pressure from 50.1 ± 15.3 mm Hg prior to support to 77.1 ± 8.0 mm Hg after support was initiated ($p$ <0.01). The cardiac index increased from 1.6 ± 0.6 L/min/m$^2$ before support to 2.3 ± 0.3 L/min/m$^2$ after support was initiated ($p$ <0.01). A total of 76 percent of the cohort (42 patients) experienced bleeding; 17 (55 percent) were successfully weaned from support, and 9 (29 percent) were discharged.[16]

In a retrospective review, the BVS 5000 was implanted in 47 patients exhibiting postcardiotomy acute heart failure. There were 38 patients in the BTR group and 9 in the BTT group. A total of 25 patients (66 percent) in the BTR group were weaned, and 16 patients (42 percent) went on to discharge. In the BTT group, 1 patient recovered myocardial function and 1 died while awaiting transplantation, although 7 patients (77 percent) underwent successful cardiac transplantation with a posttransplant survival rate of 66 percent. Patients were supported in the isolated left ventricular (28 percent), biventricular (45 percent), and right ventricular modes (28 percent).[17] In a more recent study involving 202 patients, survival at 3 days, 30 days, and 5 years was 76, 38, and 24 percent, respectively. Patients surviving 30 days experienced a 63-percent 5-year survival. A total of 48 patients (21 percent) were bridged to transplantation, and 71 patients (35.5 percent) were weaned with intent for survival.[18] Similar results are reported from other centers.[19] The wean and discharge rates is generally around 60 and 40 percent, respectively, and this approach has been shown to be cost-effective as well.[20]

***Abiomed AB5000.*** The next-generation device to follow the BVS 5000 was the Abiomed AB5000 (Fig. 51-4). This device was an updated, improved version of the BVS 5000. This pneumatically driven device utilizes the same cannulas as the BVS 5000, allowing an easy transition to this device. The AB5000 provides flows up to 6 L/min and is capable of right- or left-sided support and has a console that enables patients to become mobile within the hospital setting.

The experience with transition from BVS5000 to AB5000 in the same patient has also been good. A report of 50 patients



AB5000 Ventricle



AB5000 Console

**FIGURE 51-4** Abiomed AB5000. (With permission from Abiomed Inc.)

who initially underwent BVS5000 implantations at primary hospitals who were then transferred to tertiary care centers and were converted to the AB5000 device reported a 42 percent survival rate to either recovery, DT implantation, or transplant.[21] Of the surviving 21 patients, 18 were alive 30 days after device removal with 61 percent able to be weaned, 5.6 percent receiving a DT device, and 33 percent proceeding to transplantation.

The initial published experience with primary device implantation in patients with AMI and hemodynamic instability or postcardiotomy shock was encouraging with several patients able to be weaned from their support prior to successful hospital discharge.[22] A more recent report from the national AB5000 device registry among 100 patients who underwent AB5000 implantation for cardiogenic shock following AMI demonstrated a 40 percent 30-day survival with 63 percent successfully weaned from support, 17 percent transitioned to another support device, and 20 percent proceeded to transplantation. Of those who achieved myocardial recovery and device explantation, 2-year survival was 78 percent.[23]

## First-Generation, Pulsatile Devices

The first-generation devices have a pulsatile mode of action with flow originating from a pumping chamber separated by two valves, one for inflow and another for outflow. These are pneumatically or electrically driven and have a cyclical mode of filling and emptying.

### THORATEC VAD

The Thoratec VAD (Thoratec, Pleasanton, CA) was approved by the FDA in 1996 for use for BTT and subsequently in 1998 for BTR; this is the only approved dual-use device on the market. It was first used clinically in 1982 for postcardiotomy failure. Initially labeled the Thoratec VAD, with the subsequent development of the Thoratec implantable VAD (iVAD), this device became known as the Thoratec paracorporeal VAD (pVAD) and will be further referred to as such.

The Thoratec pVAD device is flexible and can be employed for short- or long-term use in both large and small patients because of its paracorporeal design. It is a pneumatically driven paracorporeal pump that uses Delirin tilting monostrut mechanical disk valves for maintaining unidirectional blood flow (Fig. 51-5). There is a flexible blood sac housed in a rigid outer casing; this sac is compressed by air to achieve ejection. Separate pumps are needed for each side of the heart. Three modes of operation are available: fill-to-empty, fixed-rate, and electrocardiogram (ECG)-synchronous modes. The most commonly used mode is the fill-to-empty mode, which pumps at a rate determined by VAD filling. The inflow and outflow cannulas being the only internal components, this pump can be used for small patients, including children. The cannulas are made of polyurethane except for the distal part,



**FIGURE 51-5** Thoratecparacorporeal VAD. (Reprinted with the permission of Thoratec Corporation.)

which is made of polyester Dacron. Usually CPB is needed for implantation of the cannulas. For left ventricular support, inflow can be achieved via the left ventricular apex or the left atrium; outflow is usually to the ascending aorta. For right heart support, inflow is via the right atrium and outflow is directed into the main pulmonary artery. Proper positioning of the cannulas is essential for reducing undue kinking of the cannulas and optimal device positioning on the abdominal wall. Anticoagulation with heparin followed by warfarin is required. The main limitations of this device include rather bulky paracorporeal pumping chambers and restricted patient mobility due to a large drive console.

More than 4000 patients have undergone Thoratec pVAD device implantation for left, right, and biventricular support with the longest duration of support of 1204 days. This device has been particularly useful for short-term BTT in patients suffering from biventricular failure.[24] In an analysis of 828 BTT patients, this system was used for biventricular support in 472 cases, left ventricular support in 326 cases, and right ventricular support in 30 cases for up to 515 days. During the support periods, cardiac indices increased significantly from $1.4 \pm 0.8$ to $3.0 \pm 0.5$ L/min/m$^2$ (with biventricular assistance and left ventricular cannulation). Of the 828 patients, 60 percent underwent transplantation, and the posttransplant survival rate was 86 percent. In the 195 patients who needed postcardiotomy support, the device was used for up to 80 days for cardiac recovery. Thirty-eight percent of the patients were weaned from the device, with 59 percent of these patients discharged. Of 49 postcardiotomy patients considered for transplantation, 32 underwent transplantation and 23 were discharged. Other series reflect similar results.[25,26]

Newer series also validate the earlier experiences with the pVAD. Among 84 patients who underwent pVAD implantation, 56 percent were able to wean from support or proceed to transplantation with actuarial survivals of 79, 73, and 63 percent at 1, 3, and 5 years after device implantation.[27] Another recent series with 71 patients with a total of 5193 patient-days of support had 65 percent of patients either bridged to recovery or to transplantation with actuarial survivals of 76, 68, and 62 percent at 1, 2, and 3 months, respectively.[28]

An experience with a new portable drive unit designed to allow home discharge demonstrated excellent clinical outcomes with an average discharge time of 62 days (range 16–242) and 89 percent of patients surviving to myocardial recovery and device explantation or transplantation.[29] The majority of postimplantation time (83 percent) was outpatient with significant improvement in CHF symptoms to NYHA I or II following device implantation.

Use of the pVAD for biventricular support has also been examined. Among a series of 73 patients who had ThoratecpVAD implanted as both right ventricular assist device (RVAD) and LVAD, 84 percent went on to transplantation, 10 percent were weaned and had successful device explantation, and 6 percent remained with BIVAD support.[30] Overall survival was 69 percent and 5-year survival for those receiving a heart transplant was 58 percent. For patients with high likelihood of right ventricular failure after LVAD implantation, the decision to perform both RVAD and LVAD implantation at the same time leads to improved outcomes compared with delayed BIVAD implementation.[31] Among 99 patients who underwent Thoratec BIVAD placement, there was a trend toward improved bridging to transplantation (65 vs 45 percent, $p = 0.10$) and a significantly improved survival to discharge (51 vs 29 percent, $p < 0.05$) among patients with immediate BIVAD placement compared with those who underwent delayed RVAD implantation after initial LVAD implantation. In a separate study, risk factors for eventual need of RVAD following LVAD placement included cardiac index <2.2 L/min/m$^2$, RV stroke work index <0.25 mm Hg · L/m$^2$, severe preoperative RV dysfunction, preoperative creatinine >1.9 mg/dL, reoperative cardiac surgery, and systolic blood pressure <96 mm Hg.[32]

In 2004, the FDA licensed the Thoratec iVAD for BTT, with identical features to that of the pVAD but with an intracorporeal placement (Fig. 51-6). Results from two groups have been published.[33,34] Slaughter et al. reported 39 patients who underwent placement of the iVAD who were supported for 3938 patient-days. This group was compared with a historical group of 100 patients who underwent implantation of the Thoratec pVAD device. Survival outcomes were similar for both iVAD and pVAD for BTT (70 vs 69 percent survival to transplantation) and slightly better for BTR (67 vs 48 percent survival to explant and myocardial recovery) indications, respectively. Berman et al. reported 24 patients who were supported for 2308 patient-days.[34] Survival to transplantation was 71 percent in this cohort. Taken together, these results suggest that the Thoratec iVAD has results similar to the pVAD with the advantages of its intracorporeal position. To date, more than 500 patients have undergone implantation of the iVAD device with the longest duration of support of 979 days.

## HEARTMATE LVAD

The HeartMate LVAD (Thoratec Corp., Pleasanton, CA) was designed in 1975 as an implantable, pulsatile, pneumatically actuated (HeartMate IP), intracorporeal left ventricular assist system.[35] The pneumatically driven unit is made of sintered titanium and houses a flexible, textured polyurethane



**FIGURE 51-6** Thoratecintracorporeal VAD. (Reprinted with the permission of Thoratec Corporation.)



FIGURE 51-7 HeartMate IP VAD. (Reprinted with the permission of Thoratec Corporation.)

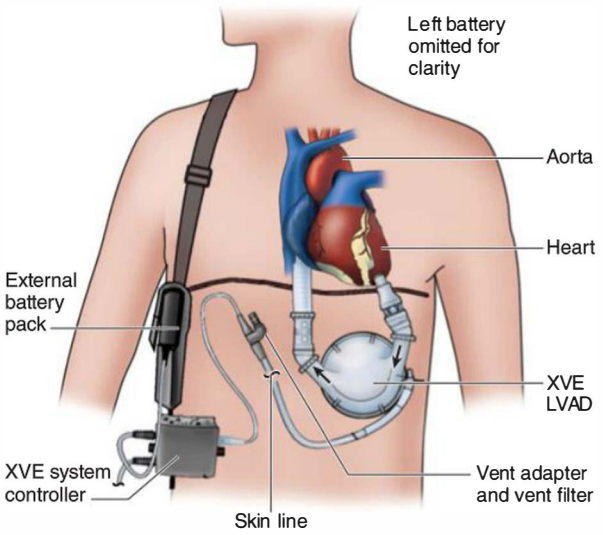



FIGURE 51-8 HeartMate XVE VAD. (Reprinted with the permission of Thoratec Corporation.)

diaphragm. It is driven by a pusher-plate mechanism that, in turn, is driven by compressed air and controlled by a console (Fig. 51-7). The design was modified to a vented electrical system (HeartMate VE) in 1991 with a much smaller console, which confers greater patient mobility.[36] The inflow and outflow conduits utilize porcine xenograft valves (Medtronic-Hancock, Minneapolis, MN). The maximum stroke volume generated is about 85 mL and maximum output can reach up to 11 L/min. The blood-contacting surfaces, unlike those of other devices, are made up of textured polyurethane, which facilitates deposition of a fibrin-collagen matrix, forming a pseudointimal layer. This feature eliminated the anticoagulation requirement, calling for aspirin only. To accommodate the device, the patient's body surface area (BSA) must to be at least 1.5 $m^2$. The pump is inserted either pre- or intraperitoneally in the left upper quadrant of the abdomen. There are two modes of operation: fixed mode (20–140 bpm for IP and 50–120 bpm for VE) and automatic mode. In the latter mode, the pump senses when its chamber is full and activates the pusher-plate mechanism (fill-to-empty). The battery life usually ranges from 4 to 6 h, with a portable hand pump backup available for device malfunction or power failure. Following the successful REMATCH trial, the enhanced version of the HeartMate SNAP-VE, the HeartMate XVE LVAS, was approved by the FDA for DT in 2002 (Fig. 51-8). The notable modification was the inflow valve conduit, which was designed to be six times more durable than in previous versions. To date, more than 1300 patients have undergone HeartMate IP LVAS implantation, although close to 2500 patients have received the HeartMate VE LVAS, with cumulative patient-years of 330 and 964 years, respectively. Over 4500 patients have received the newest HeartMate XVE device with the longest duration of support of 1864 days.

Experience from Columbia University of 243 patients undergoing implantation of HeartMate devices included 52 pneumatic, 17 dual-lead vented electrical, and 174 single-lead vented electrical devices. Overall actuarial survival rates at 1, 3, 5, and 10 years posttransplant were 90.5, 85.1, 69.6, and 39.6 percent, respectively. The overall incidence of infection was 17.7 percent ($n = 43$). Device malfunctions occurred in 32 patients.[37,38] A pivotal prospective multicenter clinical trial was conducted at 24 centers in the United States. There were 280 transplant candidates (232 men, 48 women; median age 55 years) unresponsive to inotropic drugs, intraaortic balloon counterpulsation, or both who received the device. These patients were compared with a control group of 48 patients who were not supported with a device. HeartMate VE support lasted an average of 112 days, with 54 patients supported for more than 180 days. Device-related adverse events included bleeding in 31 (11 percent), infection in 113 (40 percent), neurologic dysfunction in 14 (5 percent), and thromboembolic events in 17 (6 percent) of patients. Successful BTT was observed in 71 percent of HeartMate patients, compared with 33 percent of the control group ($p < 0.001$). A total of 198 patients survived, with

188 patients undergoing cardiac transplantation. One-year survival after transplantation was significantly better in patients who underwent LVAD implantation compared with the control population [84 percent (158 of 188) vs 63 percent (10 of 16); log rank analysis $p = 0.0197$)].[39]

A more recent report by Long et al. compared 42 patients who underwent HeartMate XVE implantation to those who received HeartMate VE devices from the REMATCH trial.[40] This study showed that there was improved survival with the newer HeartMate XVE compared with the VE (30 day: 90 vs 81 percent, 1 year: 61 vs 52 percent), as well as a decrease in adverse events. Whether the improvement in outcome was due to the advancements in technology or an improvement in patient selection and postoperative care is not known. Despite these outcomes, the HeartMate XVE has had issues with durability with device exchange or failure of 18 and 73 percent at 1 and 2 years, respectively.[38]

## NOVACOR LVAS

The Novacor LVAS (World Heart Corp., Ottawa, Canada) was developed in collaboration with Stanford University and was originally planned as a totally implantable system. It was the first device to bridge a patient successfully to transplant in 1984.[41] Over the years it evolved into a console-based VAD. The pump drive unit incorporated a dual pusher-plate sac-type pump with a smooth blood-contacting surface. The stroke volume was about 70 mL. It had two porcine-valved polyester inflow and outflow conduits. The system had a high-efficiency linear motor using a pulsed solenoid energy converter with a two-armature assembly. Thus it required no gears, cams, or intermediate hydraulic conversion, reducing the potential for mechanical failure. There were three modes of operation: single-stroke, fixed-rate, and automatic or synchronous (fill-to-empty) modes. The pump filled passively, aided by the large circular dual-pusher-plate surface area (Fig. 51-9). The power packs had 6 h of work life and could be worn on a belt, vest, shoulder bag, or backpack. Anticoagulation with warfarin was necessary and was closely monitored. The primary cause of mechanical failure was wearing out of the energy converter, although this usually was detected at least 3 months prior to its ultimate failure.[42]

The Novacor LVAS was successfully used for the past two decades as a bridge to cardiac transplantation in patients with end-stage congestive heart failure. Stanford University reported a series of 53 Novacor patients (48 male, 5 female) with a mean age of 44 years (range of 16–62 years) and a mean support time of 56 days (range of 1 to 374). Complications consisted of bleeding (43 percent), infection (30 percent), and embolic cerebrovascular events (24.5 percent). Sixty-six percent of the supported patients were successfully bridged to cardiac transplantation.[43] A recent study suggested that, in terms of durability, the Novacor device exceeded the HeartMate VE at 2 months (93.5 percent). Novacor's durability at 3 years was 85.9 percent, with 78 percent of supported patients surviving to transplantation.[44] Another study reported improvement in cardiac output, wedge pressure, pulmonary vascular resistance, and mean pulmonary pressure after Novacor implantation. Most of the complications observed were related to thromboembolism and occurred in the first 3 months after implantation.[42]

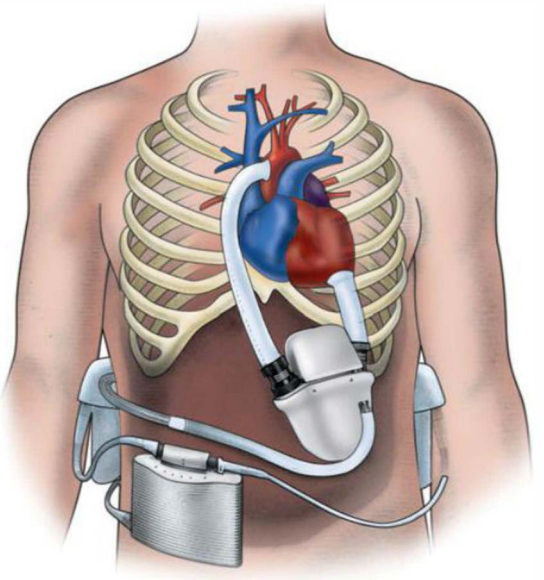


**FIGURE 51-9** Novacor VAD. (With permission from HeartWare International (for World Heart Corporation), Framingham Mass.)

The Novacor was discontinued in 2008 with later-generation devices from the same manufacturer (Levacor LVAD) taking its place.

## LIONHEART LVAS

Developed at Penn State University, the LionHeart LVAS (Arrow International, Reading, PA) was specifically designed for DT in patients with end-stage chronic heart failure.[45] The system was fully implantable without any external conduits for power. This was the first system to not require a percutaneous driveline and gave hope to the eventual development of a totally implantable device. It utilized a brushless motor that actuated a pusher plate using a roller-and-screw mechanism and Delirin disk monostrut valves. The blood-contact surfaces consisted of polyurethane sacs, which filled passively. The stroke volume was approximately 65 mL and the maximum achievable flow rates were 8 L/min. The LionHeart required a gas-filled compliance chamber implanted in the left pleural space to accommodate pump volume displacement (Fig. 51-10). In addition, there was a subcutaneous infusion port that was replaced every 2 to 4 weeks. The battery and system controller were all implanted in the right lower quadrant of the abdomen. The LionHeart's pumping characteristics, based on end-diastolic volumes, were automatically adjusted by a software algorithm, which attempted

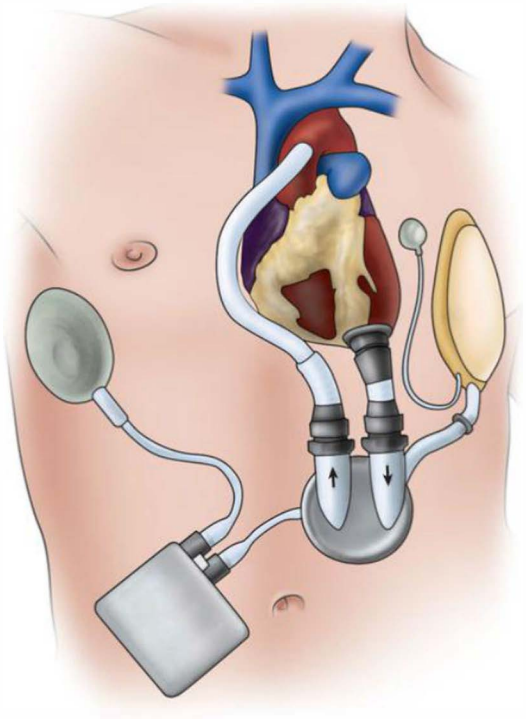


**FIGURE 51-10** Arrow LionHeart. (With permission from Arrow International.)

to provide maximal filling of the pump with each stroke by altering pump speed. The unique feature of this LVAS system was the transcutaneous energy transmission system (TETS), in which electrical energy was supplied to the pump's drive unit by radiofrequency induction. Warfarin anticoagulation was required with this device.

The first clinical implantation of the LionHeart was performed in 1999; the first implantation in the United States was performed in 2001.[46] The Clinical Utility Baseline Study (CUBS) was designed to determine the safety and performance of the LionHeart LVAS to serve as a permanent mode of circulatory support for patients with end-stage heart failure who were ineligible for heart transplantation. As a part of this trial, 26 male patients underwent implantation at seven European Centers; actuarial survival rates were 86 percent at 1 month, 45 percent at 6 months, 41 percent at 1 year, and 34 percent at 2 years.

The LionHeart LVAS was discontinued in 2005 by the manufacturer in favor of development of the newer CorAide device.

## Second-Generation, Rotary Axial Pumps

The second-generation mechanical circulatory assist devices sought to improve upon the design of the first-generation

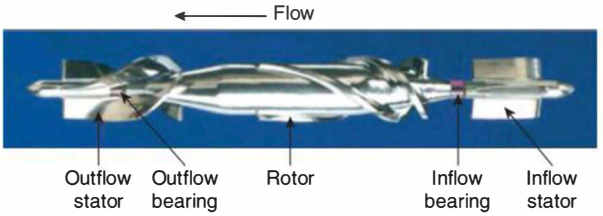



**FIGURE 51-11** Second generation axial flow pump design. (Figure courtesy of Thoratec Corporation.)

devices and to address some of the potential complications with the earlier technology. These are smaller, valveless, implantable devices that provide continuous axial flow (Fig. 51-11). An internal rotor suspended by contact bearings within the device is electrically driven by an external power source.

The first-generation pulsatile LVADs are hampered by percutaneous drivelines and bulky consoles and support systems. In addition, these assist devices are generally not suitable for patients with body surface areas of less than 1.5 $m^2$ or in pediatric patients with the exception of the ThoratecpVAD. Other characteristics of these devices include bleeding complications and difficulty in explantation. These limitations prompted the development of axial flow pumps. Technically, nonpulsatile flow pumps are more attractive than pulsatile systems because they have one moving part, permitting compactness in design, ease of insertion, and lower energy consumption. These devices are inserted into the ventricular apex (inflow) and anastomosed to the thoracic ascending or descending aorta (outflow). They do not require valves and compliance chambers, affording additional simplicity. Despite these advantages, several potential drawbacks exist. Device failure could potentially result in significant backflow of 1.5 to 2.0 L/min from the aorta into the left ventricle. Also, blood-washed bearings were not studied prior to the HeartMate II experience to adequately determine thrombogenic potential and wear characteristics. Early research showed little bearing wear and a reasonable thrombogenicity profile.[47] Furthermore, earlier concerns about the nonphysiologic nature of nonpulsatile blood flow persists, although results from rotary axial flow pumps have been encouraging. Table 51-4 summarizes the clinical data available for the second-generation devices.

### DEBAKEY VAD

The DeBakey VAD (MicroMed Technology Inc., Houston, TX) resulted from a collaboration between the Baylor College of Medicine and NASA; it is undergoing clinical trials in United States and European centers.[48,49] A small (30-mm diameter, 76-mm length, 95-g weight) titanium axial flow pump, the DeBakey VAD is based on an axial impeller–inducer supported by an inflow straightener and outflow diffuser housing ceramic blood-lubricated bearings. The pump produces a flow of 5 to 6 L/min and generates a

**TABLE 51-4: Clinical Data from Second-generation Devices**

| Device | Reference | Year | Patients | Indication (Patients) | Average Support (Days) | Longest Support (Days) | Patients Transplanted (%) | Overall Survival (Time) | Bleeding (%) | Infection (%) | Thrombosis (%) | Mechanical Pump Failure (%) | RV Failure (%) | RVAD Placement (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Heartmate II | 56 | 2009 | 18 | BTT (18) | 217 | 665 | 9 (50) | 66% (2 year) | 6 (33) | 2 (11) | 1 (6) | 0 (0) | 5 (28) | 0 (0) |
| | 57 | 2007 | 43 | BTT (23) DT (17) | 258 | >700 | 4 (17) | 80% (1 year) | 6 (14) | 3 (7) | 1 (2) | 0 (0) | 5 (12) | 0 (0) |
| | 58 | 2008 | 47 | BTT (32) DT (15) | 193 | 333 | 19 (54) | 87% (6 month) | 5 (16) | 4 (13) | 2 (6) | 1 (3) | 2 (6) | 2 (6) |
| | 59 | 2010 | 571 | BTT (417) DT (120) BTR (34) | 236 | 1019 | 96 (23) | 72% (1 year) | 95 (17) | 135 (24) | 3 (1) | 0 (0) | 36 (6) | 0 (0) |
| | 60 | 2007 | 133 | BTT (133) | 126 | 600 | 56 (42) | 68% (1 year) | 48 (36) | 55 (41) | 2 (2) | 0 (0) | 5 (4) | 5 (4) |
| | 61 | 2009 | 281 | BTT (281) | 584 | 1132 | 157 (56) | 72% (1.5 year) | 72 (26) | 130 (46) | 4 (1) | 0 (0) | 36 (13) | 17 (6) |
| | 62 | 2009 | 134 | ST (134) | NR | 730 | N/A | 58% (2 year) | 40 (30) | 47 (35) | 2 (1) | 0 (0) | 27 (20) | 5 (4) |
| DeBakey VAD | 48 | 2003 | 150 | BTT (150) | 75 | 441 | 82 (55) | 55% (NR) | 48 (32) | 5 (3) | 17 (11) | 4 (3) | 0 (0) | 0 (0) |
| Jarvik 2000 | 52 | 2003 | 26 | BTT (22) DT (4) | 67 BTT, 502 DT | 105 BTT, 889 DT | 13 (59) | 59% (NR) | NR | 0 (0) | 3 (12) | 0 (0) | NR | NR |
| | 53 | 2006 | 102 | BTT (83) DT (19) | 159 BTT, 551 DT | 986 BTT, 1789 DT | NR | NR | NR | 7 (7) | NR | 0 (0) | 0 (0) | 0 (0) |

pressure of 100 Torr at 10,000 rpm. An ultrasonic flow probe continuously measures the pump output. The inflow cannula is placed in the left ventricular apex and the outflow cannula can be anastomosed to the ascending or descending aorta. The pump is placed in a small preperitoneal pocket. A percutaneous driveline connects the power supply and control to the pump from an external console. Pump flow is nonpulsatile and requires warfarin anticoagulation. Laboratory indices reveal no significant hemolysis or changes in plasma free hemoglobin.

Worldwide experience with the DeBakey VAD includes 150 patients who underwent placement of the device as a BTT. In this series, 82 patients (55 percent) were bridged to transplantation/recovery or are currently supported and 68 patients (45 percent) died with the device.[50] Reoperation for bleeding was the most common adverse event in 48 patients (32 percent), followed by hemolysis (12 percent) and device infection (3.3 percent). Device failure occurred in four cases. Seventeen pumps (11 percent) were noted to have detectable thrombus; of these, eleven cases (64 percent) were successfully resolved with transplantation, pump exchange, or thrombolysis. Thromboembolic events occurred in 10.7 percent of patients. There is currently an ongoing clinical trial for DT (DELTA: Destination Evaluation Long-Term Assist) using the DeBakey VAD and Thoratec HeartMate XVE.

## FLOWMAKER (JARVIK 2000)

The Jarvik 2000 (Jarvik Heart Inc., New York, NY) is a titanium axial flow pump (25 mm diameter, 51 mm length, 90 g weight) that is implanted in the left ventricular apex. The outflow graft is anastomosed to either the ascending or the descending aorta depending on the surgical approach (Fig. 51-12).[51] The pump can be implanted by either a sternotomy or a thoracotomy, and with or without cardiopulmonary bypass. The lack of a pump pocket and the use of a unique postauricular connector that brings power through the infection-resistant scalp tissue behind the ear has reduced infection to less than 5% with infection rate of only .03 events/patient year. The Jarvik 2000 is available for BTT under a CAP approval and is used in a randomized destination therapy trial approved for 350 patients at up to 50 U.S. medical centers. It has CE mark and is available throughout Europe.

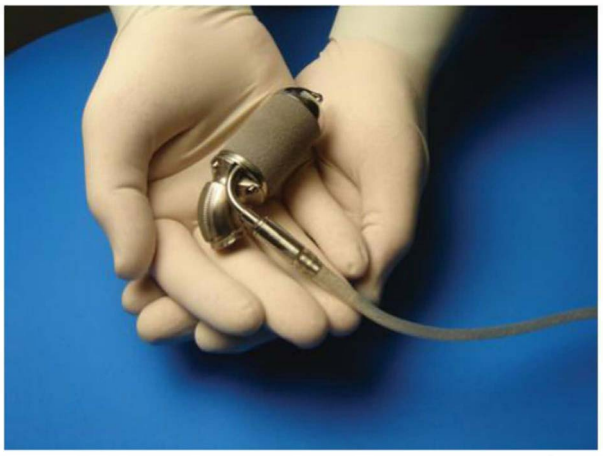


**FIGURE 51-12** The Flowmaker. (Jarvik 2000, with permission from Jarvik, Inc.)

Three different options are available for energy transmission: a percutaneous lead, a skull-mounted titanium pedestal, and Transcutaneous Energy Transfer and Telemetry System (TETTS).[51] The Flowmaker is capable of producing flows of 7 L/min at 8000 to 12,000 rpm and requires warfarin anticoagulation. Pump flow rates can be adjusted manually in times of increased activity or can be set at a fixed rate.

The first patient to receive a Flowmaker was a 61-year-old with dilated cardiomyopathy and NYHA class IV heart failure who was implanted in 2000 for DT.[52] This patient was alive and was highly functional with an improvement to NYHA class II heart failure 6 years after implantation.[53]

Frazier et al. described the experience of 26 patients who underwent implantation of a Jarvik 2000 device for BTT (22 patients) or DT (4 patients).[54] In this series 13 patients (55 percent) underwent successful transplantation after a mean support of 67 days.

Since these early reports, over 100 patients have been implanted with this device internationally.[55] Siegenthaler reported on a multicenter (European and American) experience in 102 patients who were implanted as BTT (83 patients) or DT (19 patients). There were no mechanical device failures either during in vivo use or in ex vivo bench testing over a total of 110 cumulative years (59 years in vivo, 51 years ex vivo). Mean device support times for BTT and DT were 159 and 551 days, respectively. Six of the 19 DT patients were alive for greater than 2 years and one patient nearly 5 years after implantation. The Flowmaker may prove to be a reliable, long-term solution for DT and a viable solution for BTT in appropriate patients.

## HEARTMATE II

The HeartMate II (Thoratec Corp., Pleasanton, CA) was born out of research conducted at the University of Pittsburgh in collaboration with Nimbus and has been one of the most studied devices to date. It received FDA approval for DT in 2010. It has a 40-mm diameter, 70-mm length, 176-g weight.[56] The pump mechanism is similar to that of the DeBakey VAD and Jarvik 2000. It is capable of achieving flow rates of 10 L/min and can generate 120 Torr of aortic pressure, operating at 6000 to 13,000 rpm (Fig. 51-13). The pump receives its inflow via the left ventricular apex and delivers outflow to the ascending aorta; it is placed in a small preperitoneal pocket. The current system uses a percutaneous driveline to supply power and control from an external console. Patients are maintained on warfarin anticoagulation and aspirin therapy. The first human implant was performed in 2000, and since then, the device has been evaluated by many groups.[57] The ease of implantation, small size, and nonpulsatile flow




**FIGURE 51-13** HeartMate II. (Reprinted with the permission of Thoratec Corporation.)

has made this a popular device, and results from both single institution experiences and multicenter clinical trials have established the HeartMate II as an effective device for MCS, which has revolutionized modern LVAD therapy.

Miller et al. reported the results of their prospective, multicenter clinical trial with the HeartMate II among 133 patients who received device implantation as BTT.[58] One hundred patients went on to transplantation (56 patients), continued support (43 patients), or device explantation due to myocardial recovery (1 patient). Among these patients, median device support was 126 days with an 89-percent 1-month, 75-percent 6-month, and 68-percent 1-year survival. Following successful transplantation 94 percent of patients were alive at 1 month, and 80 percent at 1 year. Heart failure was improved on device therapy as measured by both quantitative and qualitative measures. Six-minute-walk tests increased from a mean of 42 m at baseline to a mean of 292 m after 3 months of device therapy. Both the Minnesota Living with Heart Failure and Kansas City Cardiomyopathy questionnaires were statistically significantly improved at this time point as well. The most frequent complication was bleeding with 53 percent requiring transfusions greater than two units in the postoperative period and 31 percent who required re-exploration for control of hemorrhage. Rates of both for ischemic (6 percent) and hemorrhagic (2 percent) stroke were low. Rates of infection were also low with device-related infection of only 14 percent, and nondevice related infection of 28 percent. Leading causes of death were stroke (6 percent), sepsis (4 percent), and multisystem organ failure (3 percent). Rates of right heart failure were 17 percent and pump thrombosis 2 percent. Two patients who required device replacement were alive at 216 and 367 days after replacement.

In a follow-up to this trial, Pagani et al. reported the HeartMate II Investigators' extended experience among 281 patients who underwent implantation of the HeartMate II as a BTT.[59] Again, there were improvements in heart failure following 6 months of therapy; 6-min-walk test was completed in 83 percent compared with 0 percent at baseline and NYHA heart failure improved from 0 percent class I or II at baseline to 83 percent. Overall survival at 18 months was 72 percent, with 56 percent of patients undergoing transplantation, 21 percent continuing on device support, and 3 percent who experienced myocardial recovery. Again, the most common adverse event was bleeding in 53 percent, and mediastinal re-exploration in 26 percent. Infection was the next most common with nondevice infection in 30 percent, device infection in 14 percent, and sepsis in 17 percent. Stroke rates were low at 8 percent (5 percent ischemic, 3 percent hemorrhagic). Right heart failure was 17 percent and pump thrombosis was only 1 percent.

Another trial reported by the HeartMate II investigators was for use of this device as DT among patients with advanced heart failure.[60] This trial compared the nonpulsatile HeartMate II and the older-generation, pulsatile HeartMate XVE. Patients with advanced heart failure refractory to maximal medical support and who were ineligible for cardiac transplantation were included. Patients with significant pulmonary, hepatic, or renal dysfunction were excluded. The primary endpoint was survival at 2 years without stroke or reoperation for device exchange. Secondary endpoints included actuarial survival, adverse events, functional status, and overall quality of life. The HeartMate II demonstrated a clear improvement in outcome compared with the HeartMate XVE with regard to the primary endpoint (46 vs 11 percent at 2 years). In addition, events that prevented patients from reaching the primary endpoint such as reoperation to repair or replace the pump (10 vs 36 percent) or any reason overall (54 percent vs 89 percent) were statistically different among the HeartMate II and HeartMate XVE groups, respectively. Actuarial survival rates at 1 and 2 years were significantly better with the HeartMate II than the HeartMate XVE as well; 68 percent vs 58 percent and 55 vs 24 percent, respectively, among the groups.

Both groups experienced improvements in NYHA class heart failure, increased performance on the 6-min-walk test, and improved quality of life following device implantation. At baseline, all patients had severe heart failure, including 75 percent who had NYHA class IV heart failure in the HeartMate II group and 78 percent in the HeartMate XVE group. For the HeartMate II group, after 12 months of device support 76 percent of patients were improved to NYHA class I or II, and by 24 months 80 percent of patients were improved to NYHA class I or II heart failure in 42 percent and 38 percent, respectively. In the HeartMate XVE group after 12 months, 61 percent were improved to NYHA class I or II, and by 24 months the remaining surviving patient had NYHA class I heart failure. Six-minute-walk times were improved from a mean of 182 to 372 m for the HeartMate II group and from 172 to 306 m for the HeartMate XVE group. Results from both the Minnesota Living with Heart Failure and Kansas City Cardiomyopathy questionnaires were also significantly improved from baseline, the former

being statistically better with the HeartMate II and the latter approaching significance between the groups.

Rates of adverse events with the HeartMate II were also significantly decreased compared with the HeartMate XVE, including both device and nondevice infection, right heart failure, arrhythmias, and respiratory and renal failure. The leading causes of death were hemorrhagic stroke (9 vs 10 percent) and right heart failure (5 vs 8 percent) in both groups, HeartMate II and XVE, respectively. Bleeding requiring transfusions occurred in 81 and 76 percent and that requiring re-exploration in 30 and 15 percent among the HeartMate II and HeartMate XVE, respectively. Pump thrombosis was more common in the HeartMate II group at 4 percent, compared with no patients in the HeartMate XVE group.

Frazier et al. reported the Texas Heart Institute experience with the HeartMate II in 43 patients, 23 for BTT and 17 for DT.[61] In this initial experience, the average support time was 258 days and 35 survived to hospital discharge including 3 patients who underwent transplantation and 4 patients who had myocardial recovery and pump explantation. Ongoing support was reported in 27 patients with the longest greater than 700 days. Cardiac index was significantly improved and pulmonary capillary wedge pressures were reduced in all patients, and inotropes were removed by 1 week following implantation. All patients improved to NYHA class I status following implantation. There were 9 deaths; 5 died from multifactorial causes (multisystem organ dysfunction, right heart failure, and hemorrhage) and two patients suffered strokes.

John et al. reported an experience in 47 patients who received the HeartMate II for BTT (32 patients), DT (7 patients), or exchange for a prior device (8 patients) demonstrating excellent results: 96-percent 30-day and 87-percent 6-month survival among patients receiving a HeartMate II and mean support time of 193 days with a 3-percent incidence of device malfunction.[62] Among those patients who received a HeartMate II for BTT, 60 percent were transplanted and all survived to discharge. Renal and hepatic function were both significantly improved after 3 months of device therapy. The most common complications were bleeding in 32 percent, half of whom required re-exploration, followed by infection in 13 percent. Right ventricular failure and pump thrombosis were uncommon, each occurring in 6 percent of patients. Stroke was equally uncommon, occurring in only 6 percent of patients.

Lahpor et al. reported the European experience among three centers and 571 patients implanted as BTT (73 percent), DT (21 percent), and BTR (6 percent).[63] Mean support was 236 days with support greater than 6 months, 1 year, and 2 years of 61, 29, and 3 percent, respectively. Survival at 6 months was 74 percent and at 1 year was 72 percent. In this group, 23 percent proceeded to transplantation, 42 percent have continued support, and 4 percent underwent device explantation following myocardial recovery. The most frequent cause of death was multifactorial in nature (sepsis, right heart failure, followed by stroke). Bleeding occurred in 51 percent and was not a source of mortality. There were only three device thromboses, and right heart failure occurred in 20 percent.

Loforte et al. reported the Italian experience with the HeartMate II among their 18 patients who underwent implantation for BTT.[64] In this group, the median support time was 217 days with the longest supported patient having continued support 665 days after implantation. Fifty percent of patients proceeded to transplantation with 67 percent alive after transplantation at last following. There were no device failures, and the most common complications were bleeding in 33 percent, right ventricular failure in 28 percent, infection in 11 percent, and thrombosis in 6 percent. There were no reported device failures.

This device has also been reported as use for BTT in the pediatric population, with two adolescents (12 and 14 years of age) being supported for 85 and 128 days before successful implantation.[65]

## Third-Generation, Centrifugal Continuous Flow Pumps

The potential hemolytic consequences of having rotor bearings in contact with blood in the second-generation devices led to the development of the most recent, or third-generation devices. These have been designed without any components in direct contact with the bloodstream, using hydrodynamic or magnetic levitation to suspend an internal rotor that provides centrifugal, continuous flow. Table 51-5 summarizes the clinical data available for the second-generation devices.

### VENTRASSIST LVAS

The VentrAssist (VentraCor Limited, Chatswood NSW, Australia) is a small implantable centrifugal pump designed for DT and BTT. It uses a hydrodynamic rotor suspension, which avoids areas of slow and turbulent blood flow. The absence of bearings reduces rotor wear, enhancing the device's durability. It uses large rare-earth magnets with small gaps and a harmonic drive system. Weighing 298 g, it is 6 cm in diameter and 6.5 cm in length. The externally worn battery and controller provide power and control; the battery holds sufficient charge for up to 8 h. The small size of the device will permit its use in smaller adults as well as in children. The short inflow cannula connects to the left ventricular apex and the outflow cannula is anastomosed to the ascending aorta. It has a low potential for thrombosis due to a reduction of stasis and therefore requires minimal anticoagulation. This device has been studied in several multinational clinical trials.

Several smaller clinical trials evaluated the feasibility of using the VentrAssist for both BTT and DT (Pilot Trial, 9 patients; Pivotal Trial, 44 patients; US Feasability Study for BTT, 7 patients) from 2003 to 2005.[66] Results from these smaller trials were encouraging with no device

**TABLE 51-5: Clinical Data from Third-generation Devices**

| Device | Reference | Year | Patients | Indication (Patients) | Average Support (Days) | Longest Support (Days) | Patients Transplanted (%) | Overall Survival (Time) | Bleeding (%) | Infection (%) | Thrombosis (%) | Mechanical Pump Failure (%) | RV Failure (%) | RVAD Placement (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VentrAssist | 64 | 2007 | 30 | BTT (30) | 167 | 486 | 25 (83) | 87% (1 year) | 5 (15) | 11 (33) | 4 (12) | 1 (3) | 1 (3) | 1 (3) |
| LVAS | 65 | 2008 | 33 | BTT (33) | 197 | 646 | 20 (61) | 82% (1 year) | 9 (24) | 19 (58) | 8 (15) | 0 (0) | 4 (12) | 1 (3) |
| | 66 | 2010 | 412 | BTT (412) | NR | 1533 | 148 (36) | 81% (NR) | NR | NR | NR | NR | NR | NR |
| DuraHeart | 68 | 2008 | 35 | BTT (35) | 330 | 808 | 14 (40) | 78% (2 year) | NR | NR | 0 (0) | 0 (0) | NR | NR |
| LVAS | 69 | 2009 | 68 | BTT (68) | 242 | 1148 | 18 (26) | 61% (2 year) | 8 (24) | 18 (55) | 0 (0) | 0 (0) | 9 (27) | 1 (3) |
| Heartware | 71 | 2010 | 23 | BTT (23) | 167 | 425 | 5 (22) | 86% (1 year) | 7 (30) | 11 (48) | 6 (26) | 0 (0) | 1 (4) | 1 (4) |
| HVAD | 76 | 2010 | 99 | BTT (99) | 251 | 1108 | 22 (22) | 80% (2.5 year) | NR | NR | NR | NR | NR | NR |
| | 77 | 2010 | 140 | BTT (140) | NR | NR | NR | 91% (1 year) | NR | NR | NR | NR | NR | NR |
| EVAHEART LVAD | 78 | 2008 | 14 | BTT (14) | 337 | 866 | 0 (0) | 78% (2 year) | NR | NR | 0 (0) | 0 (0) | NR | NR |
| INCOR | 79 | 2008 | 212 | BTT (212) | 162 | 1071 | 65 (31) | 66% (NR) | NR | NR | NR | 0 (0) | NR | NR |

failures over a cumulative device time of 33 years and a median support time of 180 days. Among the 33 patients who underwent device implantation for BTT, 82 percent were alive at the 5-month trial endpoint with 40 percent having undergone heart transplantation and another 42 percent alive and awaiting transplantation.[66] Results for the 16 patients who received a device as DT were equally good; 1- and 2-year survivals were 80 and 60 percent.[67] Recently the international experience with the VentrAssist device implanted in over 400 patients has been published.[68] Among 412 patients who underwent device implantation, 81 percent reached the endpoint of transplantation (36 percent), continued support (44 percent) or myocardial recovery (1 percent) and the longest period of support was in a patient who was alive with greater than 4 years of continuous support.

The future of this device, however, is uncertain. In 2009, following the deaths of three patients due to damaged electrical leads, the company temporarily stopped all new implantations. Following this event, the company manufacturing the device declared bankruptcy, and was liquidated as clinical trials were underway.



FIGURE 51-14 DuraHeart LVAS. (From Terumo Corporation, with permission.)

## DURAHEART LVAS

The DuraHeart LVAS (Terumo Heart, Inc., Ann Arbor, MI) is an active magnetically levitated centrifugal pump. The impeller is levitated by three electromagnets, and rotation is achieved by magnetic coupling between the impeller and the motor. The pump weighs 540 g, displaces 196 mL, and can generate flows up to 8 L/min (Fig. 51-14) at 120 mmHg head pressure with no residual left ventricular function.[69] The heparin-bonded inflow and outflow cannulas and pump blood chamber comprise the blood contacting surfaces. Warfarin anticoagulation is recommended. The device is commercially approved in Europe and Japan. Clinical trial enrollment was closed in December 2011 for a Pivotal BTT FDA investigation.

The initial clinical experience with the DuraHeart was a European, multicenter trial of 33 patients who underwent device placement for BTT.[70] This group had no device mechanical failures over a cumulative support duration of 28.7 patient-years.[71] Forty-two percent of patients went on to receive a heart transplant at a mean of 185 days. For those that remained on support awaiting transplant, a 2-year survival was 57%. An updated experience reporting on 82 European patients who underwent implantation of the DuraHeart showed no pump replacements after 6 months over a cumulative support time of 78 years and a median duration of support of 261 days.[71] Survival at 6 months and 1 year were 85 and 79%, respectively. The longest duration of support, at the time of the publication, was more than 4.1 years.

## HEARTWARE HVAD

The Heartware HVAD (Heartware International, Framingham, MA) is a continuous flow, centrifugal pump that is small enough (4 × 2 cm, 50 mL displacement) to be implanted in the pericardial space yet is capable of generating flows up to 10 L/min (Fig. 51-15). The only moving part is the impeller that is suspended directly in the bloodstream within the pump itself using magnetic and hydrodynamic thrust bearings, thus eliminating any physical contact between the impeller and the pump. The inflow cannula is integrated into the device itself that is placed directly into the apex of the heart, and the distal end is anastomosed to



FIGURE 51-15 Heartware HVAD. (With permission from HeartWare International (for World Heart Corporation), Framingham Mass.)

the ascending aorta. Implantation can be achieved through median sternotomy or left thoracotomy with or without the use of CPB. Warfarin anticoagulation is required. This device has been studied for use as both BTT and DT in the United States and internationally.

This device was initially evaluated in an international multicenter clinical trial in Europe and Australia among 23 patients with implantation as BTT.[72,73] The mean duration of support was 167 days (range 13–425 days) and actuarial survival at 6 months and 1 year were 91 and 86 percent. By the 180-day endpoint 2 patients underwent transplantation, 19 patients had continued device support, and successful weaning and device explantation occurred in one patient in this trial. A case report noted complete resolution of heart failure symptoms up to 6 months after explant.[74] Three groups have also reported successful biventricular support with the DuraHeart as well, with up to 189 days of successful support.[75–77]

Long-term data from the clinical experience among 99 patients implanted in Europe were equally promising.[78] The mean duration of support was 251 days with support longer than 6 months in 26 patients and support longer than 1 year in 6 patients. Among this group of patients, 22 were successfully transplanted, 4 were weaned and underwent device explantation, and 61 remained on support with a longest continuous support time of 1108 days. The actuarial survival was 80 percent at 2 years.

In addition, this device recently has been examined in a multicenter clinical trial in the United States for use as BTT. The ADVANCE study enrolled 140 patients on the heart transplantation list at 30 centers across the United States and was designed as a noninferiority analysis comparing the Heartware HVAD to previously approved and commercially available devices. These patients were compared with 499 patients from the INTERMACS registry who underwent implantation of any available device during the same period. Survival of the study group was 92 percent at 180 days and 91 percent at 1 year, compared with 90 percent and 86 percent in the control group, thus establishing the Heartware HVAD as comparable to existing devices for BTT.[79]

The ENDURANCE trial is currently underway and has been designed to enroll 450 patients at 50 centers across the United States to examine the application of this device for DT in a randomized, controlled fashion among patients with advanced heart failure.

## EVAHEART LVAD

The EVAHEART LVAD (EVAHEART Medical, Pittsburgh, PA) is a centrifugal pump device with a unique thromboresistant coating over the surfaces of the pump housing, the impeller, and the cannula in order to reduce thrombotic and thromboembolic complications associated with device implantation. This device is implanted in the preperitoneal position and is capable of generating flows up to 14 L/min. Current clinical trials that began in 2010 are underway to evaluate this device for BTT applications.



**FIGURE 51-16** INCOR. (From Berlin Heart, Inc., with permission.)

Initial clinical trials in Japan among 14 patients who received EVAHEART devices as BTT demonstrated good results.[80] Over a cumulative device support time of 12.9 years there were no device failures and 6-month, 1-year, and 2-year survivals were 91, 78, and 78 percent, respectively. Support times of >1 year were reported in 43 percent, and over 2 years in 21 percent of patients. This device is currently being investigated in clinical trials in the United States.

## INCOR

The INCOR (Berlin Heart Inc., The Woodlands, TX) is a magnetically levitated, fully implantable axial flow pump. The impeller is capable of rotating at a speed of 12,000 rpm and can generate flows of 7 L/min at pressures up to 150 mm Hg (Fig. 51-16). The INCOR requires about 8.5 W of power, weighs 200 g, and is 30 mm in diameter. The pump is titanium-based with silicone conduits. Anticoagulation is with warfarn and aspirin. The battery and power pack weigh about 1.5 kg and can be carried on one's person, with a TETTS energy transfer system. This device is currently in clinical trials in the United States that began in 2009.

This device has been implanted in 212 patients for various indications in European clinical trials with good results.[81] No pump failures were reported and patients had a mean duration of support of 182 days. Eventual outcomes were transplantation in 31 percent, continued support in 20 percent and device explantation in 5 percent.

## LEVACOR

The Levacor LVAD (WorldHeart Corp., Salt Lake City, UT) is a continuous flow, centrifugal rotary pump with an impeller suspended by magnetic levitation. Despite a low profile (maximum dimensions of 38 mm) it is capable of generating flows up to 10 L/min (Fig. 51-17). Warfarin anticoagulation is required. It is implanted in a preperitoneal location with inflow cannula placed in the left ventricular apex and



FIGURE 51-17 Levacor. (With permission from HeartWare International (for World Heart Corporation), Framingham Mass.)

outflow cannula anastomosed to the ascending aorta. This has been an evolution from the Novacor and the prototype HeartSaver and is the latest device in this series. This device has been successfully implanted in an early feasibility study and is currently under investigation in a United States BTT clinical trial.[82]

## Total Artificial Heart

### SYNCARDIA (CARDIOWEST) TOTAL ARTIFICIAL HEART

The Syncardia (formerly called CardioWest) TAH (Syncardia Inc., Phoenix, AZ) was developed at the University of Utah by Robert Jarvik. Its precursor, the Jarvik 7, was implanted by DeVries in 1980.[7] This is a pneumatically driven biventricular pulsatile device, which is implanted orthotopically.[83] It consists of two ventricular chambers connected to the native atria and incorporates a 27-mm Medtronic-Hall mechanical tilting-disk valve (inflow). The blood-contacting surface consists of an air-compressed polyurethane sac (Fig. 51-18). The pneumatic hose and drive line exit transcutaneously to a console that controls the pump and delivers the compressed air. The pump delivers a stroke volume of 70 mL and is capable of achieving a maximum flow rate of 8 L/min. Warfarin anticoagulation is required. A strict size criterion is observed in selecting patients for this device (Table 51-6). Limitations of this device include the large, cumbersome console and frequent maintenance of the pneumatic inlets and outlets, although recently three patients have been successfully discharged to home with portable drivers. It is currently FDA approved for BTT.

Since its introduction, over 850 devices have been implanted internationally for BTT indications with a cumulative experience of greater than 190 patient-years.[84] The initial feasibility studies were conducted in a multicenter trial in the United States.[85] Inclusion criteria for this trial were: eligibility for transplantation, NYHA class IV heart failure, BSA 1.7 to 2.5 $m^2$ and hemodynamic insufficiency classified as either CI <2.0 L/min/$m^2$ or conventional cardioactive drugs at maximal dose with or without IABP or use of CPB. Exclusion criteria were any prior use of VAD, pulmonary hypertension with pulmonary vascular resistance >640 dyne·sec·$cm^2$, dialysis in previous week or serum creatinine >5 mg/dL, cirrhosis with bilirubin >5 mg/dL, or presence of cytotoxic antibodies. In this trial, 81 patients who received the Syncardia TAH were compared with 31 patients who met inclusion criteria but who did not receive any MCS. Rates of survival to transplantation were significantly



FIGURE 51-18 Syncardia TAH. (With permission from SynCardia Systems, Inc.)

**TABLE 51-6: CardioWest Total Artificial Heart: Criteria for Implantation**

| |
|---|
| Body surface area ≥1.7 $m^2$ |
| Cardiothoracic ratio >0.5 |
| Left ventricular diastolic dimension >66 mm |
| Anteroposterior distance (sternum to T10, by computed tomography) >10 cm |
| Combined ventricular volume (measured by computed tomography) >1500 mL |

improved in the Syncardia TAH group compared with the control group, 79 vs 46 percent, $p$ <0.001. One-year survival rates were also improved with the Syncardia TAH compared with the control group, 70 vs 30 percent, $p$ <0.001. Overall 1- and 5-year survival for patients who received the Syncardia TAH as BTT therapy was 86 and 64 percent, respectively. Among all patients, there was one device failure that resulted in a patient death.

A follow-up study by Leprince et al. reported a single institution experience of 127 patients implanted with the Syncardia TAH over a 15-year period.[86] There was one device failure in 3606 cumulative device support days. Rates of survival to transplantation increased over time with 43 percent before 1993, 55 percent between 1993 and 1997, and 74 percent reaching transplantation after 1997.

An analysis based upon the initial experience of 81 patients in the United States trial was recently published in an attempt to identify which patients might benefit from this device.[87] The authors of this study found that independent predictors of mortality were a history of smoking or coagulopathy with PT >16 s in the implant to posttransplant period. Interestingly these were different risk factors for mortality than previously reported for LVAD or separate biventricular support devices which are right heart failure, previous mediastinal operations, mechanical ventilation before implantation, and end organ dysfunction of the renal, hepatic, or pulmonary organ systems.



**FIGURE 51-19** Abiocor TAH. (With permission from ABIOMED, Inc.)

## ABIOCOR TOTAL ARTIFICIAL HEART

The AbioCor TAH (ABIOMED Inc., Denver, MA) is inserted orthotopically after excising the native ventricles. The energy converter is situated between the two ventricles and consists of a high-efficiency miniature centrifugal pump.[88] A two-position switching valve is used to alternate the direction of the hydraulic flow between the right and left pumping chambers, thus alternating systole between the two chambers. The stroke volume of each chamber is 70 mL (Fig. 51-19). Pumping rates can be adjusted between 75 and 150 bpm with a resultant flow rate of 4 to 8 L/min. All blood-contacting surfaces of the AbioCor TAH, including the trileaflet valves, are made of polyether urethane, resulting in a smooth, continuous blood-contacting surface. An atrial balance chamber permits adjustment of stroke volumes and maintains balance between right and left chambers. This unique feature obviates the need for a compliance chamber. The energy transfer is achieved by TETTS. The controller and the battery modules (Ni-Cad) are implanted preperitoneally. Externally worn components include the TETTS primary and Ni-Ion battery modules. Anticoagulation with warfarin is required. This device is available as a Humanatarian Device Exemption from the FDA and has been investigated in a clinical trial.

Initial data from clinical trials of the AbioCor TAH have been reported. Inclusion criteria were patient age of 18 years or more, ineligibility for cardiac transplantation, a high likelihood of dying within 30 days while on optimized medical management, an acceptable device-fitting evaluation, and biventricular failure with inability to be weaned from temporary MCS. Exclusion criteria were heart failure with significant potential for reversibility, patients on chronic dialysis, irreversible liver failure, blood dyscrasias, suspected or active systemic infection, a positive serum pregnancy test result, severe peripheral vascular disease, transient ischemic attack or stroke secondary to atherosclerosis, psychiatric illness (including drug or alcohol abuse), and lack of an adequate social support system. All patients had a 30-day predicted mortality of more than 70 percent based on the AbioScore prognostic model or acute myocardial infarction shock scores. The AbioScore mortality prediction model was developed based on previous prognostic models, including measurements that had the highest prognostic value for mortality in patients with end-stage heart failure. These factors include age, serum sodium, renal function, need for inotropic or intra-aortic balloon pump support, body-mass index, left ventricular end-diastolic diameter, peak exercise oxygen consumption, and New York Heart Association (NYHA) functional class. Eligible candidates were screened for device fitting using a proprietary software program (AbioFit, ABIOMED).[89] The primary end point of these first trials was the AbioCor's impact on all-cause mortality in patients with severe heart failure and a predicted life expectancy of less than 30 days despite optimized medical management. Secondary end points included a determination of adverse events, device malfunction, complications related to the device, and quality of life. Thusfar, 14 implants have been

performed in the United States, with most of the patients completing 60 days successfully.[88,89] The preliminary results revealed two intraoperative deaths (due to intraoperative bleeding or aprotinin reaction) and four late deaths (one from multisystem organ failure and three related to cerebrovascular accidents). Six patients recovered to the point of being able to take multiple trips outside of the hospital, with two patients reaching hospital discharge.[87] There has been one long-term survivor with this device, and no implantations have occurred since 2004.

### Penn State TAH

The Penn State TAH (ABIOMED Inc., Danvers, MA) was developed at Penn State University with funding from the National Heart, Lung, and Blood Institute (NHLBI), and later developed with a corporate partnership with Abiomed. It is a fully implantable, orthotopically placed biventricular electromechanical total replacement system. The pump consists of a rigid titanium casing enclosing polyurethane blood sacs and an energy converter. This device utilizes Delirin monostrut valves to provide unidirectional flow.[90] The energy converter is composed of a brushless DC electric motor, which actuates a roller screw with pusher plates. Mechanical compression of the blood sacs by the pusher plates against the rigid housing results in alternate emptying of the blood. It has low associated vibrations and minimal noise. It has a stroke volume of about 64 mL and can reach a maximum output of about 8 L/min. Physiologic sensing is through the end-diastolic volume estimated from the motor speed and voltage; this provides the balance between the left- and right-sided pump outputs (akin to the LionHeart). The energy source is comprised of TETTS and quick-charging Ni-Cad batteries. A compliance chamber is connected to the motor housing and implanted internally. This device has undergone preclinical testing, feasibility, and durability studies, but no clinical data in patients have been published.[90]

## NEWER DEVICES

There are several, newer-generation devices that are being developed for clinical use. The majority of these are in preclinical in vitro bench studies and in in vivo animal studies and have either not yet proceeded to clinical use or have little published data on their use in patients.

### HeartQuest VAD

The HeartQuest VAD (MedQuest Products Inc., Salt Lake City, UT) is an implantable, centrifugal pump housed in a titanium casing. It uses magnetic levitation to suspend and drive a self-centering impeller. The inflow cannula is placed in the left ventricular apex with the outflow cannula anastomosed to the ascending aorta. This device can provide 1.5 to 9 L/min of blood flow. It has a bench durability of 5 years, with low anticoagulation requirements.[91]




**FIGURE 51-20** HeartMate III. (Reprinted with the permission of Thoratec Corporation.)

### HeartMate III

The HeartMate III (Thoratec Corp., Pleasanton, CA) is a fully implantable, magnetically suspended centrifugal pump. It incorporates the textured blood surface used in previous Thoratec devices. It measures 6.9 cm by 3.5 cm, has a displacement volume of 195 mL, and weighs 500 g (Fig. 51-20). This device produces a mean blood flow of 4.3 L/min (±1.5 L/min) and is powered by TETS[69] Bench studies have shown up to 40 months of continuous use without device failure.[92]

### TandemHeart pVAD

The TandemHeart pVAD (CardiacAssist Technologies, Inc., Pittsburgh, PA) is a centrifugal pump that can be rapidly deployed by cardiologists in the cardiac catheterization laboratory by femoral arterial access. It is light in weight (280 g) and requires only 7 mL of priming fluid to accommodate



**FIGURE 51-21** TandemHeart. (From CardiacAssist, Inc, with permission.)

both small and large patients (Fig. 51-21). It is intended for reversible causes of cardiac failure following percutaneous revascularization.[91] The pump is powered by a stationary electromagnetic motor, which drives a rotor and impeller. Rotating at 2700 to 4700 rpm, it is capable of generating flows up to 6 L/min and pressures up to 90 mm Hg. Heparin anticoagulation is required during support.

Burkhoff et al. randomized 42 medical patients with cardiogenic shock to receive the TandemHeart pVAD or conventional IABP therapy.[93] Although the TandemHeart pVAD was associated with significant improvements in cardiac index, MAP, and PCWP, there were no differences in 30-day survival or adverse outcomes between the groups.

Recently, this device has been investigated for use in postcardiotomy shock in a BTR fashion.[94] Initial feasibility studies were completed in 11 patients with a mean duration of support of 88 h. Nearly three-quarters of all patients could be weaned from the device and 55 percent survived to discharge. Survival at 1 and 4 years were 46 and 36 percent, respectively.

## AB-180 iVAD

The AB-180 iVAD (CardiacAssist Technologies, Inc., Pittsburgh, PA) is a surgically implantable version of the TandemHeart pVAD (described above). A 10-mm polytetrafluoroethylene (PTFE) graft conducts outflow to the aorta. A percutaneous cable connects to an integrated infusion pump delivering lubrication and anticoagulation fluid, a flow estimator, and a power line to the VAD. This device can be deployed for postcardiotomy syndrome, acute myocarditis, and acute postinfarction myocardial failure and shock.[95,96]

## Kriton VAD

The Kriton VAD (Kriton Medical, Miramar, FL) is a small centrifugal pulsatile device that is fully implantable. The impeller of the pump is supported by a passive radial magnetic bearing that acts in synergy with hydrodynamic bearings. Torque is transmitted to the impeller by electromagnetic coupling via an integrated axial flux gap motor. It can displace 48 mL and generate an output up to 15 L/min. Weighing only 195 g with an extracardiac volume of 28 mL, this device is intended for long-term use and has undergone extensive preclinical testing.[97]

## CorAide LVAS

Developed at the Cleveland Clinics, the CorAide LVAS (Arrow Int., Reading, PA) is a small continuous-flow centrifugal pump. It has a magnetically suspended rotor, weighs 293 g, and capable of generating blood flows up to 6 L/min. It replaced the LionHeart LVAS in 2005. In preclinical trials, it has shown promise without requiring anticoagulation.[98] Thusfar it has been implanted in European trials in five patients with successful outcomes out to 6 months having been reported.[99]

## Kantrowitz CardioVad

The Kantrowitz CardioVad (LVAD Technologies Inc., Detroit, MI) has three main parts: a blood pump that is implanted on the lateral aspect of the descending thoracic aorta, a connector for an external power source, and a drive unit to power the pump. The pump, an inflatable avalvular polyurethane bladder, is sutured in place after excising a lateral portion of the aorta. It is about 6.5 cm in length and capable of displacing 60 mL of blood when inflated. The blood-contacting surface is textured so that pseudointima may form on it.[100] No anticoagulation is needed and an external air pump mounted in the external drive unit inflates and deflates the blood pump synchronously but out of the phase with heart contractions. The diastolic augmentation reduces left ventricular afterload, increases cardiac output, and improves coronary perfusion.

Initial feasibility studies among the first five patients showed that this device significantly increased cardiac index by 36 percent and decreased heart failure symptoms (NYHA IV to II) while improving renal function.[100] An updated clinical experience with this device among 9 patients had a range of duration of support from 2 to 458 days with a total support time of 1082 days, 557 of which were spent out of the hospital.[101]

## Pittsburgh Streamliner Mixed Flow Pump

The Streamliner, the first magnetic-bearing LVAD, is named for the way it provides minimal disturbance to blood flow. Developed at the McGowan Center for Artificial Organ Development, a subdivision of the Department of Surgery at the University of Pittsburgh School of Medicine, the



FIGURE 51-22 EXCOR. (From Berlin Heart, with permission.)

Streamliner operates at approximately 7500 rpm, supplementing the action of a weak or damaged heart.[96]

## Excor

The EXCOR (Berlin Heart Inc., The Woodlands, TX) is a pneumatically actuated paracorporeal pump that can support both ventricles (Fig. 51-22). The EXCOR stroke volume ranges from 10 to 80 mL, permitting its use in adults and children. It is available with two alternative types of valve systems: a mechanical tilting disk and a polyurethane velum valve. The cannulas are made of silicone and are designed to reduce the incidence of thromboembolism and entry/exit site infections. There are two systems available for pneumatic support. One is a stationary drive and the other is a mobile unit. The stationary unit (called Ikus) is capable of supporting both ventricles and can run in synchronous and asynchronous modes; each ventricle can be operated independently. The mobile unit (called Excor) weighs 8.7 kg with two power packs and features a physiologically adaptive synchronous operation. Preliminary studies in children have shown this device to be useful as BTT and BTR therapy in this patient population.[102,103]

## Abiomed Impella

The Abiomed Impella (Abiomed Inc., Danvers, MA) is a catheter-based device that is inserted into the aorta, across the aortic valve into the left ventricle (Fig. 51-23). The Impella LP 2.5 is designed for placement through femoral arterial access by interventional cardiologists in the angiography suite, and

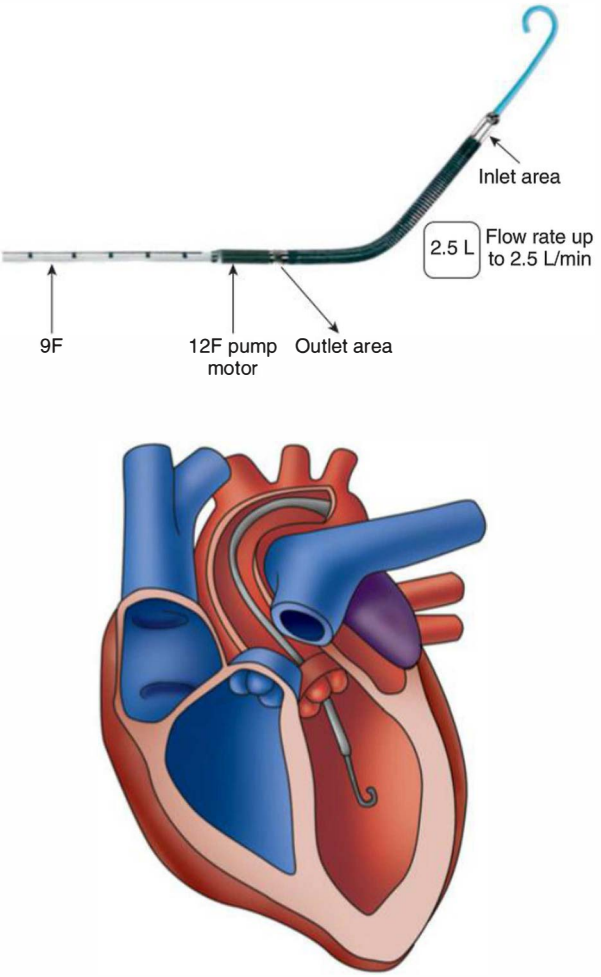



FIGURE 51-23 Abiomed-Impella. (From ABIOMED, Inc., with permission.)

the LP 5.0 by cardiac surgeons through either aortotomy or the femoral/axillary artery. Current indications include high-risk percutaneous coronary interventions, postcardiotomy heart failure, and cardiogenic shock following acute myocardial infarction. Preliminary data demonstrated an improvement in survival compared to IABP for patients with postcardiotomy heart failure.[104]

## Levitronix Centrimag

The Levitronix Centrimag (Levitronix Inc, Waltham, MA) is a short-term, extracorporeal device that provides continuous flow via a centrifugal pump (Fig. 51-24). It is capable of delivering flows up to 9.9 L/min and has a contact-free magnetically-levitated impeller without mechanical bearings or seals (Fig. 51-23).



**FIGURE 51-24** LevitronixCentrimag. (Levitronix Corp., with permission.)

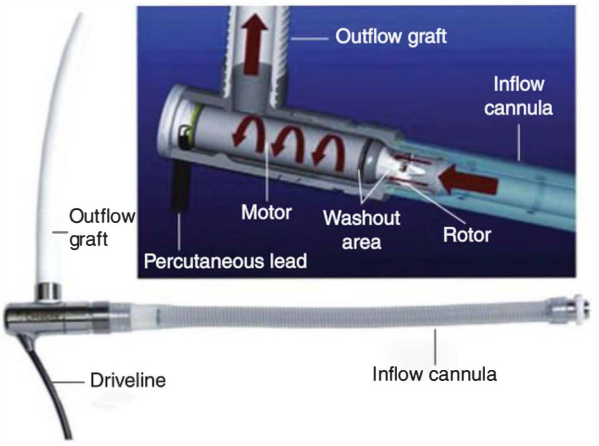



**FIGURE 51-25** Circulite LVAS. [Reproduced with permission from Meyns BP, Simon A, Klotz S, et al. Clinical benefits of partial circulatory support in New York Heart Association class IIIb and early class IV patients. *Eur J Cardiothorac Surg.* (Epub ahead of print.)]

This device is currently under clinical investigation in an ongoing trial, the Centrimag Pivotal Trial, led by the Thoratec Corporation. Preliminary data in 12 patients with cardiogenic shock following acute myocardial infarction that was refractory to maximal medical management demonstrated a successful bridge to definitive procedure (coronary revascularization, long-term VAD placement) or recovery with 56 percent of patients discharged from the hospital and a 1-month survival of 67 percent.[105]

## Circulite

The Circulite (Circulite, Saddle Brook, NJ) is the smallest implantable device for long-term support and is the size of a AA battery (Fig. 51-25). This device was specifically designed to provide partial support to patients with class IIIb and early class IV NHYA heart failure, and is capable of flows up to 3 L/min. This device has an inflow cannula placed into the left atrium and an outflow graft placed into the right subclavian artery that are implanted without CPB through a mini-thoracotomy incision. Current prototypes in development will feature completely percutaneous placement of the inflow cannula via a transseptal system and outflow cannula to the subclavian artery via an anastomotic connector.

This device has been examined in a clinical trial conducted in Europe.[106,107] Among 35 patients in this group, the mean support time was 5 months with the longest greater than 14 months and survival was 91 percent to either hospital discharge or transplantation. Of these patients, 14 were successfully bridged to transplantation at a median time of 3.5 months. Physiologic parameters, including cardiac index, mean arterial pressure, and PCWP were all increased, and pulmonary artery pressures were decreased following device implantation. A trial in the United States is planned for 2011.

## Other Devices

Other devices in development, preclinical, and in some cases early clinical testing are the MiTi Heart VAD (MiTi Heart Corporation), MagScrew for VAD and TAH (Foster Miller Technologies), and an external cardiac support device called ParaCor (Paracor Surgical Inc.). Other heart failure support devices that alter the geometry of the left ventricle are the CorCap Cardiac Support Device (Acorn Cardiovascular Inc.) and the Myosplint System (Myocor Inc., Maple Grove, MN).[108,109]

# PATIENT SELECTION

Currently, MCS can be considered for BTR, BTT, and DT. Consideration is based on the indication for support and the operative risk involved for the patient. Profound heart failure due to chronic congestive heart failure or acute postcardiotomy pump failure are the most common indications for the institution of MCS. Candidates for support typically display clinical indices of chronic heart failure, with PCWPs in excess of 20 mm Hg, cardiac indices less than 2.0 L/min/m$^2$, and systolic blood pressures less than 80 mm Hg despite inotropic support.

For BTR indications, including postcardiotomy failure, short-term support with a centrifugal pump or a pulsatile

paracorporeal device is appropriate, since these devices are relatively easy to implant and maintain. If necessary, these devices can be exchanged for longer term pulsatile or axial flow devices. The option of implanting a TAH for DT is still impeded by the limited experience with these devices, but as experience grows, TAH and the smaller axial flow devices with portable consoles may be suitable devices for these patients.

## PREOPERATIVE RISK FACTORS FOR VAD THERAPY

One of the first studies to identify risk factors predictive of postoperative outcomes in VAD patients used a weighted assessment of 24 individual variables in a series of 26 patients.[110] Different types of devices were used, with 70 percent of the subjects receiving biventricular support. The risk factors most strongly associated with adverse outcomes included age greater than 50 years, preoperative cardiopulmonary resuscitation, mechanical ventilation or $FIO_2$ greater than 70 percent, ECMO, and blood urea nitrogen greater than 60 or a serum creatinine greater than 2.2 mg/dL.[110] Similarly, a review of 56 patients from the Cleveland Clinics and Columbia Presbyterian Hospital between 1990 and 1994 identified oliguria, central venous pressure greater than 16, mechanical ventilation, coagulopathy, and repeat sternotomy as risk factors.[111,112] Survival associated with VAD implantation also correlated well with APACHE II scores, which were significantly improved in patients supported by LVADs. Survival times determined by Kaplan–Meier analysis and Cox proportional analysis after adjustment for APACHE II scores were better for MCS ($p$ <0.02).[113]

A multivariate analysis of 464 VAD patients obtained from the Novacor European Registry revealed that independent risk factors for death after device implantation included respiratory failure associated with septicemia, right heart failure, age greater than 65 years, acute postcardiotomy failure, and acute myocardial infarction. In the absence of any risk factors, the 1-year survival rate was 60 percent, including posttransplant survival. Any risk factors reduced survival rates to 24 percent.[114] In a prospective multicenter clinical trial conducted at 24 centers in the United States with 280 transplant candidates treated with the HeartMate XVE LVAD, increasing age, prior heart surgery, and hepatic/renal dysfunction were the major predictors of adverse outcomes following device implantation.[39] In a retrospective analysis of 97 LVAD patients, including 64 pneumatic devices and 36 electric devices, significant risk factors for death included a preoperative need for ventilator support or ECMO, elevated blood urea nitrogen, elevated serum creatinine, hyperbilirubinemia, and low pulmonary artery pressures. Postoperative risk factors included reoperation for bleeding, RVAD support requirement, dialysis, and device failure.[115]

**TABLE 51-7: Columbia University and Cleveland Clinics Scoring System for Predicting Mortality after LVAD Implantation**

| Variable | Score |
|---|---|
| Revised system | |
| Ventilation | 4 |
| Redo surgery | 2 |
| Previous LVAD insertion | 2 |
| Central venous pressure >16 mm Hg | 1 |
| Prothrombin time >16 s | 1 |
| Original system | |
| Urine output <30 mL/h | 3 |
| Ventilation | 2 |
| Central venous pressure >16 mm Hg | 2 |
| Prothrombin time >16 s | 2 |
| Redo surgery | 1 |

In 1995, Columbia University and the Cleveland Clinics proposed a scoring system to predict successful outcomes after LVAD implantation; it was further expanded with evolving technology (Table 51-7).[111,116] The scoring system is based upon 130 patients who received the vented electrical HeartMate device from 1996 to 2001 (Table 51-8). A score higher than 5 corresponds with a 47 percent mortality, compared with a 9 percent mortality for a score less than 5 (79 percent positive predictive value vs 70 percent negative predictive value).[116]

## CARDIAC CONSIDERATIONS

### Valvular Heart Disease

Valvular stenosis and regurgitation often have significant implications for assist device function. Mitral stenosis can lead to impaired LVAD filling and flow rates. A competent aortic valve is necessary for proper LVAD function; severe aortic regurgitation should be corrected with device implantation. Mild-to-moderate aortic regurgitation can worsen once left ventricular support is initiated because of a reduction in left ventricular pressure and an increase in aortic root pressure. VADs do not completely unload the left ventricle, leading to some flow across the aortic valve. This low, intermittent flow is inadequate to wash an existing mechanical aortic prosthesis. Many feel that mechanical valves should be replaced by bioprosthetic valves at LVAD implant to prevent thrombus formation and subsequent embolism.

### Right Ventricular Function

When significant right ventricular dysfunction exists, biventricular support should be considered. If right ventricular failure is not recognized prior to the implantation of left ventricular support, unique problems can arise that may

**TABLE 51-8: Factors Important in Selecting a Mechanical Assist Device**

| Factor | Device |
|---|---|
| Duration of support | |
| Short term | Centrifugal pumps |
| | Paracorporeal devices (e.g., Thoratec VAD, ABIOMED BVS 5000) |
| Short- to medium term | Ventricular assist devices (Novacor, HeartMate, LionHeart) |
| Long term | Ventricular assist devices (e.g., Novacor, HeartMate, LionHeart) |
| | Total artificial heart (e.g., AbioCor TAH, CardioWest TAH) |
| Aim of support | |
| Bridge to transplant | Centrifugal pumps |
| | Paracorporeal devices (e.g., Thoratec VAD, ABIOMED BVS 5000) |
| | Ventricular assist devices (e.g., Novacor, HeartMate, LionHeart) |
| Bridge to recovery | Ventricular assist devices (e.g., Novacor, HeartMate, LionHeart) |
| | Axial flow pumps (e.g., DeBakey, HeartMate II, Jarvik 2000) |
| Destination therapy | Ventricular assist devices (e.g., Novacor, HeartMate, LionHeart) |
| | Axial flow pumps (e.g., DeBakey, HeartMate II, Jarvik 2000) |
| | Total Artificial Heart (e.g., AbioCor, CardioWest) |
| Type of support | |
| Univentricular | All devices |
| Biventricular | Paracorporeal devices (Thoratec VAD, ABIOMED BVS 5000) |
| | Total Artificial Heart (e.g., AbioCor, CardioWest) |
| Technical factors | |
| Small body size | Axial flow devices (e.g., DeBakey, Jarvik 2000, HeartMate II) |
| Size of device | |
| Anticoagulation | Extracorporeal pumps |

necessitate a device change and possibly lead to significant morbidity and mortality.[117] Unfortunately, current biventricular support devices are cumbersome, with large consoles limiting patient mobility. Preoperative risk factors for right ventricular failure after LVAD insertion include hyperbilirubinemia, elevated creatinine, and mechanical ventilatory support.[118] Ochiai and colleagues found that several factors had an 80 percent predictive value in determining the need for right ventricular assistance: right ventricular end-diastolic dimension of 8.5 cm, right ventricular end-diastolic volume of 200 mL, a mean pulmonary artery pressure of 60 mm Hg, and a mean right atrial pressure of 70 mm Hg.[119]

## Atrial and Ventricular Arrhythmias

Atrial fibrillation and atrial flutter can lead to inadequate right ventricular filling and thrombus formation. Both cardioversion and anticoagulation are essential, even if the device does not otherwise require anticoagulation. Ventricular arrhythmias can be considered as a relative contraindication for mechanical support, although it has been shown that device flow can be maintained adequately during ventricular fibrillation in the setting of low pulmonary vascular resistance. In conclusion, arrhythmias should be treated prior to VAD implantation.

## Intracardiac Shunts

Because of the significant right-to-left shunting that can result after unloading the left ventricle, it is important to close any patent foramen ovale or atrial septal defects at the time of assist device implantation.

# OTHER CONSIDERATIONS

Noncardiac organ function plays an important role in clinical outcomes with mechanical device support. Also important is the timing of device insertion, but this is largely influenced by the referral pattern, institutional preferences, and surgeon-specific factors. Some poor outcomes following device therapy are due to delay in instituting device implantation. Ideally, device implantation should be considered prior to the onset of organ failure.

## Pulmonary Function

Although there are no consensus criteria for pulmonary function testing prior to assist device implantation, a $FEV_1$ greater than 50 percent predicted, FVC of 50 percent predicted, and $DL_{CO}$ of 50 percent predicted are usually baseline requirements in selecting candidates for mechanical support. Although LVAD therapy has been shown to reduce pulmonary vascular resistance, this is not always observed. When pulmonary vascular resistance is fixed, unloading of the left ventricle by the device does not lead to a significant reduction of right ventricular afterload and increased pulmonary blood flow. In patients with severe pulmonary disease, preoperative computed tomography of the chest is warranted.

## Renal Function

Many studies have identified renal dysfunction as a significant predictor of poor outcomes following assist device implantation. A thorough preoperative evaluation of renal dysfunction is important to determine reversibility. A candidate's baseline renal function prior to the onset of cardiac failure or cardiogenic shock and the potential for recovery should be considered. Many centers now employ aggressive renal support via hemodialysis and hemofiltrationwhich, to

some extent, has made many patients suitable for mechanical device therapy who would otherwise have been denied. An elevated creatinine has been shown to be a negative risk factor for LVAD insertion.[120] Similarly, elevated blood urea nitrogen greater than 40 mg/dL has been shown to be a risk factor for BTT survival. Severe right ventricular dysfunction and volume overload with a right atrial pressure above 20 mm Hg can lead to changes in glomerular filtration, with a resultant decrease in urine output and resistance to diuretic therapy.

### Hepatic Function

Significant hepatic dysfunction or failure can be detrimental in assist device patients. Prolongation of the international normalized ratio (INR) is one of the most significant risk factors for complications in mechanical assist patients, associated with significant perioperative bleeding and transfusion requirements, worsening coagulopathy, right ventricular dysfunction, and multiorgan-system failure.[121] A total bilirubin greater than 3.6 mg/dL or a direct bilirubin greater than 1.2 mg/dL (e.g., cardiac congestion, drug toxicity, hepatitis, alcohol abuse) is an independent risk factor for adverse outcomes.[122] If these markers are found to be elevated in a candidate's evaluation, a thorough investigation to assess the degree and severity of hepatic dysfunction is warranted. Patients with right heart failure with resultant hepatic congestion may need right ventricular support in addition to left ventricular support. These and other considerations are particularly important when DT is being considered.

### CNS Function

The potential for postoperative long-term rehabilitation after device insertion is based on an understanding of the workings of the device, consoles, various alarms, and device maintenance. Hence a major irreversible neurologic deficit or cognitive impairment, which would render patients incapable of managing their devices, is generally a contraindication for device implantation. However, limited motor deficits are not singular contraindications to mechanical device support; in such cases, determinations should be made in consultation with neurologists and support staff.

## DEVICE SELECTION

The selection of a mechanical support device is largely dependent on the candidate's clinical situation. Selection is first and foremost dependent on the duration of support needed (e.g., short-, medium-, or long term); the aim of support (i.e., BTT, BTR, or DT); whether univentricular or biventricular support is needed; patient size (many devices are limited to a BSA >1.5 $m^2$); and the size of the device itself, particularly when pediatric support is being considered. Anticoagulation requirements and the degree of support represent important secondary issues. Long-term durability and mechanical robustness are important factors when DT is considered. How some of the factors determine device selection is outlined in Table 51-8. A decision-making flowchart for device selection is offered in Figure 51-26.

## SURGICAL MANAGEMENT

### Preoperative Preparation

As outlined earlier, every attempt should be made to optimize distal organ function. Common interventions include IABP, diuresis, pulmonary vasodilators (e.g., prostaglandin $E_1$), hemodialysis/hemofiltration, and the replacement of coagulation factors. A right atrial pressure below 12 mm Hg, PCWP less than 20 mm Hg, and cardiac index greater than 2.0 are target indices prior to insertion of the device. Pre- or intraoperative echocardiographic studies can help identify a patent foramen ovale or small atrial septal defect and assess valvular and ventricular function.

### Operative Technique

Most VADs are implanted through a median sternotomy on CPB (Fig. 51-27).[123] The devices can be placed within intra- or preperitoneal pockets. A preperitoneal pump pocket is created by extending the median sternotomy incision. The size of the device affects its location in many patients. Early attempts at placing the device intraperitoneally resulted in colonic perforations, intestinal obstruction, and diaphragmatic hernias; this has led most surgeons to place these devices extraperitoneally. Care is taken to achieve meticulous hemostasis during pocket construction, since hemorrhage and the formation of pocket hematomas are among the most common complications. After the pocket is created, the device is primed and the driveline tunneled from the pocket to exit the right upper abdominal quadrant. The patient is then heparinized and the heart cannulated for CPB. An off-pump end-to-side anastomosis between the aorta and the outflow conduit can be performed in some patients using a partially occluding clamp. Left ventricular apical inflow cannulation is typically performed on CPB, creating a circular apical ventriculotomy, placing circumferential mattress sutures to anchor an apical connector, and connecting the LVAD inflow cannula to this connector. Some surgeons feel that apical inflow cannulation should be performed first to permit more accurate sizing of the outflow graft. Once the inflow and outflow connections have been made, the LVAD chamber is passively filled, followed by pump de-airing maneuvers. CPB is then weaned concomitantly with initiation of VAD function.

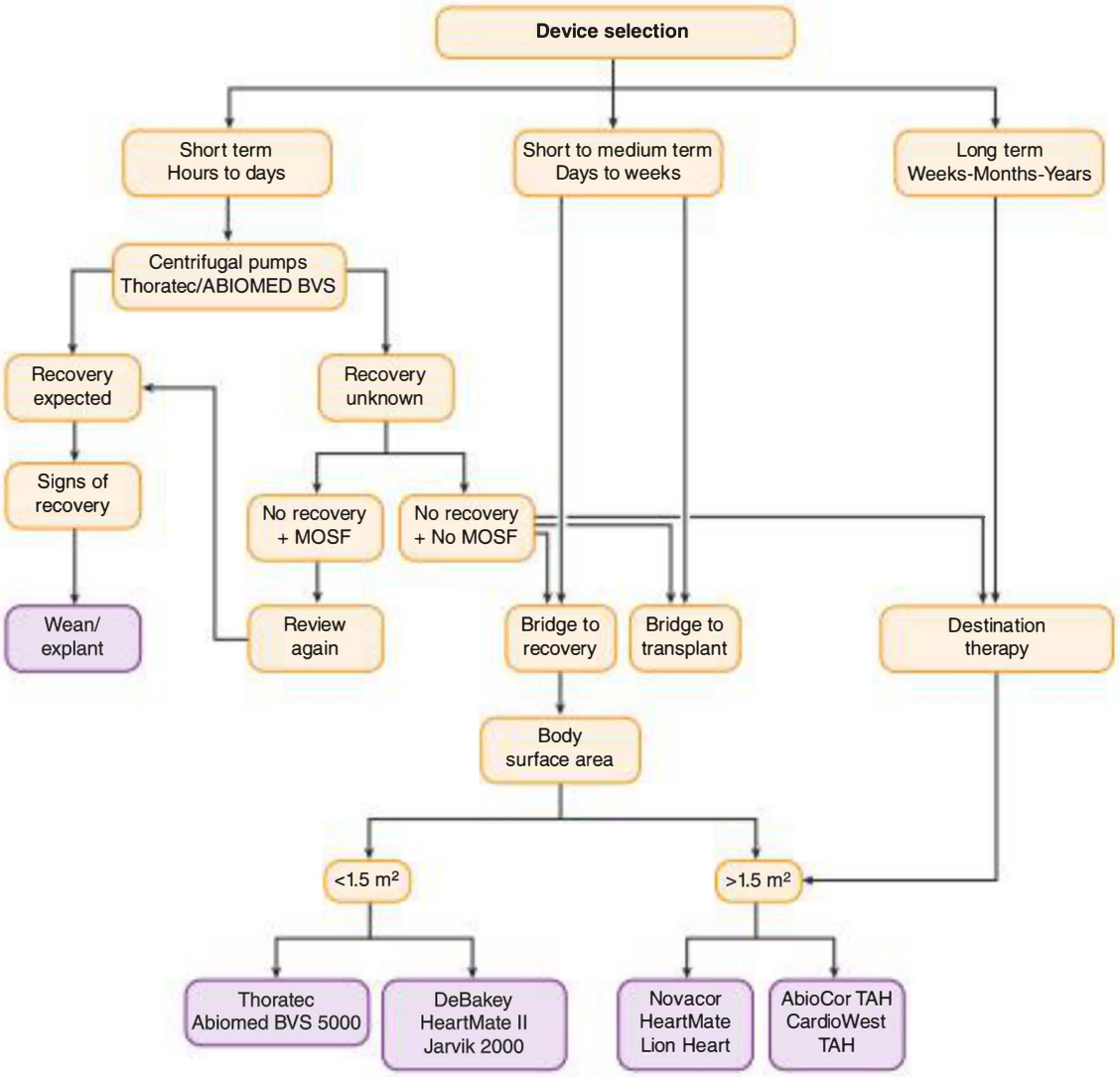



**FIGURE 51-26** Decision-making flowchart: device selection.

In addition, VAD implantation may be performed via median sternotomy without CPB. Off-pump VAD implantation at some centers has been associated with decreased operative times, ventilator time, inotropic support, and hospital stay compared to traditional on-pump VAD implantation.[124]

Several alternative methods exist for VAD implantation with different operative exposures, including subcostal and left thoracotomy approaches. These techniques are useful among patients who have had prior sternotomies and/or patent coronary bypass grafts that may be injured during median sternotomy, who need device exchange, or who otherwise may not tolerate the dissection needed for the traditional median sternotomy. These approaches may all be performed without CPB, but for each of these techniques, appropriate vascular exposure in the groin or chest should be obtained in case the need for emergent CPB arises. Subcostal approaches have been described with and without CPB for initial implantation or device exchange with good results (Fig. 51-28).[125–127] Device implantation through a left thoracotomy has also been employed, both on- and off-pump, with similar success (Fig. 51-29).[128–131]

## Postoperative Care

After LVAD implantation, early postoperative care focuses on optimizing and monitoring native right ventricular function in addition to the usual ICU procedures following cardiac surgery. Adequate right heart function can be fostered with pulmonary vasodilators (e.g., milrinone, nitric oxide).

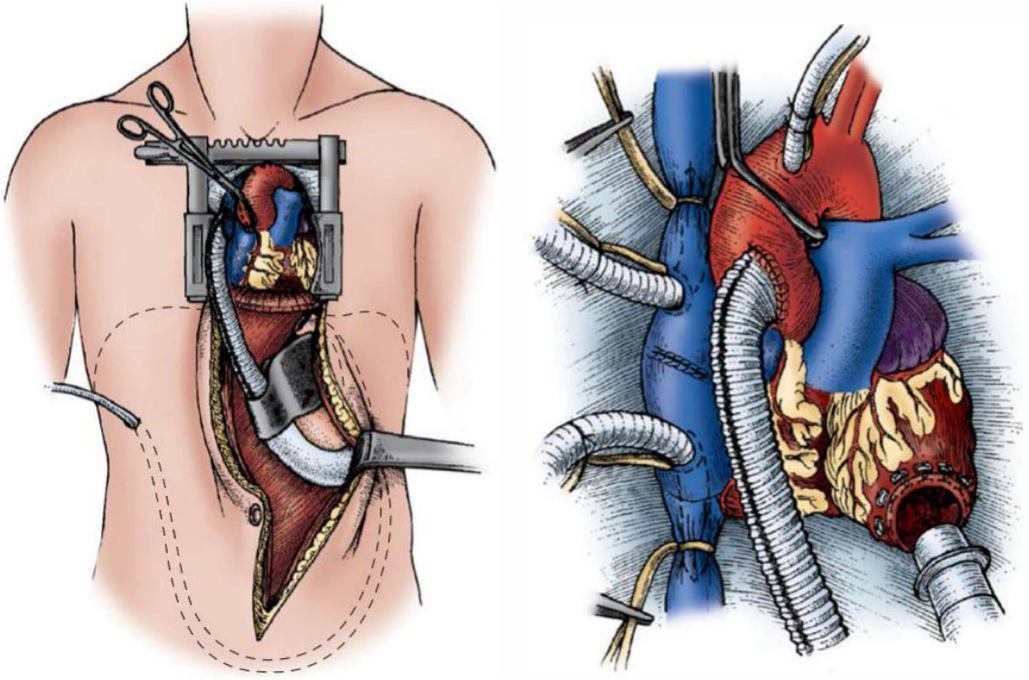


**FIGURE 51-27** Implantation of the Novacor LVAS via median sternotomy approach. (Reproduced with permission from Loisance D, Cooper GJ, Deleuze PH, et al. Bridge to transplantation with the wearable Novacor left ventricular assist system: Operative technique. *Eur J Cardiothorac Surg* 1995;9:95–98.)

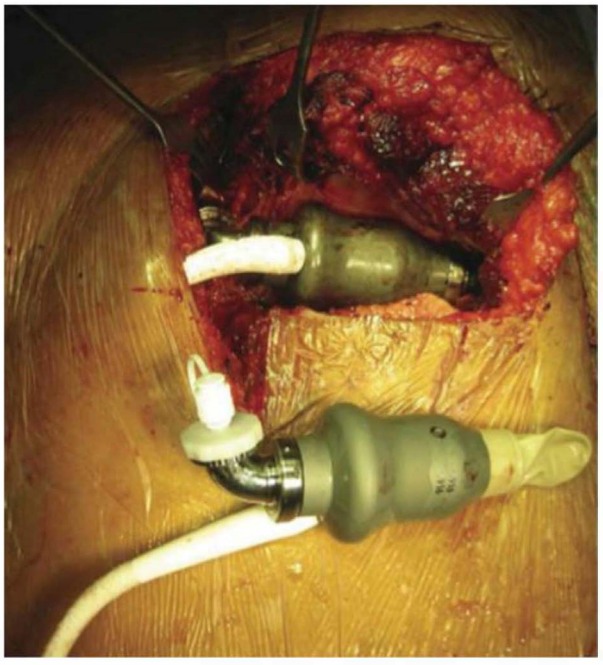


**FIGURE 51-28** Subcostal technique for device implantation. (Reproduced with permission from Woo YJ, Acker MA. Implantable ventricular assist device exchange with focused intravascular deairing techniques. *Ann Thorac Surg* 2011;91:306–307.)

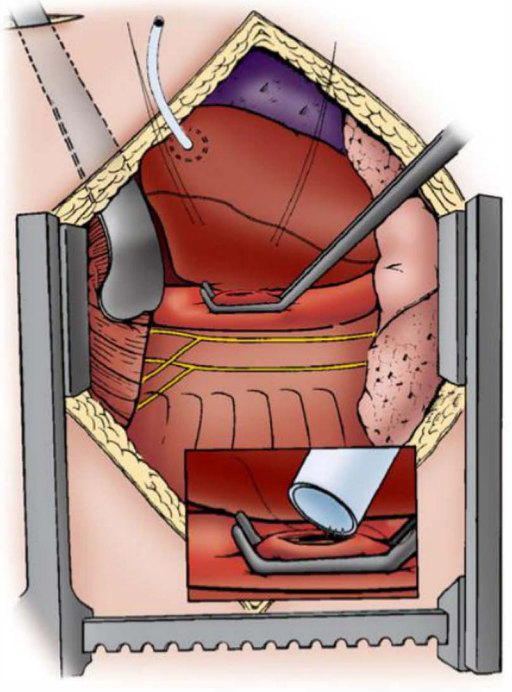


**FIGURE 51-29** Device implantation via left thoracotomy. (Reproduced with permission from Pierson RN, Howser R, Donaldson T, et al. Left ventricular assist device implantation via left thoracotomy: Alternative to repeat sternotomy. *Ann Thorac Surg* 2002;73:997–999.)

Patients can be weaned to extubation once hemodynamics have been stabilized and hemostasis has been assured. Following this, early patient mobilization and nutritional repletion are undertaken. Heparin is typically used early postoperatively with long term anticoagulation regimens usually consisting of aspirin and warfarin.

### VAD Explantation

In BTT patients, VAD explantation at the time of transplantation can be complicated by dense adhesions around the device conduits. This situation can be somewhat ameliorated by wrapping the conduits with Gore-Tex. Regardless, upon reentry through the sternum, care must be taken to avoid damage to underlying cardiac and device structures.

## COMPLICATIONS

### Bleeding

Hemorrhage is the most common complication after assist device implantation.[26,132] Technical factors that can lead to increased bleeding include the creation of large pockets for device placement, loose device connectors and conduits, and insufficient hemostasis (e.g., cannulation sites, sternal edges). Bleeding can be caused by coagulopathy due to liver failure, prior antiplatelet and antithrombotic medications, and CPB-related platelet consumption.[112] Consequently, meticulous hemostasis, a low threshold for re-exploration, and judicious use of blood products and clotting factors are mandatory in device implantation. Nevertheless, once medical causes for hemorrhage have been corrected (hypothermia, thrombocytopenia, coagulopathy), if significant bleeding (>200 $cm^3$/h from chest tubes) or tamponade physiology develop, return to the OR for reassessment is indicated.

The incidence of significant bleeding was reported to be as high as 50 percent in early series, with up to 60 percent of patients undergoing re-exploration for hemorrhage.[26,132–134] With newer-generation devices in the most recent two clinical trials, postoperative transfusion of any blood products occurred in 76 to 81 percent, significant transfusion (>2 units) occurred in 53 percent, and reoperation for bleeding occurred in 30 to 31 percent.[58,60] Delayed sternal closure has been advocated by some in cases of severe coagulopathy or right heart dysfunction, with closure 24 to 48 h after device implantation to allow for achievement of hemostasis and recovery of right heart function prior to closure of the median sternotomy.[135]

### Infection

The reported incidence of device-related infections varies, but remains one of the most frequent complications after bleeding.[26] Among the first-generation devices, infection rates ranged from 49 to 66 percent and rates of significant sepsis were reported up to 41 percent.[26,136] The lack of standardized definitions and criteria for device-related infections have rendered reported infection rates rather inexact.[137] Rates of infection with the newer devices are significantly improved; however, this continues to be a source of morbidity and mortality. The third annual report of the Mechanical Circulatory Support Device Database of the International Society for Heart and Lung Transplantation reports an overall infection incidence of 32.5 percent with a 7.9 percent mortality rate.[138] Among clinical trials of newer devices, rates of localized infection (not device related) range from 28 to 49 percent, percutaneous lead infection of 14 percent, LVAD infection of 35 percent, and sepsis from 20 to 36 percent.[58,60] The risk of infection has been shown to be related to device and operator experience among retrospective reviews.[139,140]

### Thromboembolism

Thrombosis is associated with all devices, and can lead to device failure or distal thromboembolism. Historically, device implantation was associated with a thromboembolism incidence of 10 to 25 percent among early devices.[141] Better conduits that promote neointimal growth have reduced thromboembolic complications; nevertheless even the newer-generation devices, including axial flow and TAH devices, also suffer from thromboembolic complications. Among current devices, device thrombosis has been low at 2 to 4 percent, with distal thromboembolic events (mainly stroke) occurring in 7 to 8 percent of patients.[58,60]

### Multisystem Organ Failure

Multisystem organ failure after VAD implantation often results from preexisting unrecognized organ dysfunction. On the other hand, infection leading to sepsis, excessive hemorrhage, blood product transfusions, and prolonged ventilation can also contribute to postoperative multisystem organ failure. The incidence of postimplantation organ failure is reported to be between 10 and 30 percent. Careful preoperative assessment and proper timing for device insertion should serve to reduce this incidence.

### Right Ventricular Failure

Approximately 7 to 39 percent of patients experience some degree of right ventricular failure at the time of LVAD implantation.[142] Mechanisms for this phenomenon have been proposed. concomitant underlying right ventricular dysfunction may exist and may be unmasked at the time of LVAD implantation. Even nondysfunctional right ventricles are more sensitive to acute and significant changes in afterload with left ventricular device implantation. An increase in

**Predictors of right ventricular failure on multivariable analysis**

| Study | Definiton of RVF | Patients with RVF, *n* (% of sample) | Preoperative variables analyzed | Multivariable predictors |
|---|---|---|---|---|
| Ochiai et al. [8] | RVAD | 23 (9) | Demographics, echo, laboratory values, cardiopulmonary hemodynamics | Preop. MCS, female gender, nonischemic cardiomyopathy |
| Dang et al. [5] | RVAD, ≥14 d of inotropes, vasodilators, or both | 42 (39) | Patient demographics, pre- and intraop. cardiopulmonary hemodynamics | Intraop. RA pressure |
| Matthews et al. [9•] | RVAD, ≥14 d of inotropes or discharge on an inotrope, ≥48 h of inhaled NO | 68 (35) | Demographics, echo, laboratory values, cardiopulmonary hemodynamics, vasoactive medications | Preop. vasopressor requirement, Cr ≥2.3 mg/dL, AST ≥80IU/L, bilirubin ≥2.0 mg/dL |
| Fitzpatrick et al. [24•] | RVAD | 99 (37) | Demographics, echo, laboratory values, cardiopulmonary hemodynamics | Cardiac index ≥2.2 L/min/m$^2$, RVSWi 0.25 mm Hg/m$^2$/beat, prior sternotomy, SBP ≤96 mm Hg, severe RV dysfunction on echo, Cr ≥1.9 mg/dL |
| Drakos et al. [19•] | RVAD, ≥14 d of inotropes or discharge on an inotrope, ≥48 h of inhaled NO | 77 (44) | Demographics, echo, laboratory values, cardiopulmonary hemodynamics, vasoactive medications | Destination therapy, IABP, PVR quartile, inotrope dependence, BMI ≥30, ACE inhibitor/ARB use, β-blocker use |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AST, aspartate amniotransferase; BMI, body mass index; Cr, creatinine; echo, echocardiogram; IABP, intr-aortic balloon pump; MCS, mechanical circulatory support; NO, nitric oxide; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; RVAD, RV assist device; RVF, RV failure; RVSWi, RV stroke work index; SBP, systolic blood pressure.

**FIGURE 51-30** Risk factors for development of right ventricular failure after device implantation. (Reproduced with permission from Romano MA, Cowger J, Aaronson KD, et al. Diagnosis and management of right-sided heart failure in subjects supported with left ventricular assist devices. *Curr Treat Option Cardiovasc Med* 2010;12:420–430.)

cardiac output leads to increased venous return to the right heart, and transfusion and other vasoactive agents can lead to pulmonary vasoconstriction, leading to right heart failure. Early right ventricular failure after LVAD implantation can lead to poor filling of the LVAD, low pump outputs, and systemic hypoperfusion. Significant primary right ventricular failure has been defined as a right atrial pressure greater than 20 mm Hg on maximal drug support or a right atrial pressure greater than the PCWP. Occasionally, severe right ventricular failure necessitates placement of an RVAD to sustain LVAD output. Patients who develop right ventricular failure following device implantation have higher morbidity (increased ICU stay, renal failure, coagulopathy) and short- and long-term mortality rates (up to 38–43 percent) compared to those who do not.[142]

Multiple studies have identified various preoperative risk factors and devised risk stratification profiles for right ventricular failure following LVAD placement.[142] Clinical factors include older age, female sex, lower body surface area, redo sternotomy, postcardiotomy heart failure, nonischemic cardiomyopathy, and implantation for DT as risk factors for the development of right ventricular failure after device implantation. Other factors include preoperative evidence of right ventricular dysfunction (high RA pressures with or without pulmonary systolic hypertension, low right ventricular stroke work index, echocardiographic findings, hepatic congestion), cardiogenic shock with inotropic or intraaortic balloon pump support, and multisystem organ failure. The use of newer continuous flow devices may be related to a reduced risk of right heart failure.[143] A summary of risk factors identified by several groups on multivariate analysis and their related risk stratification profiles are outlined in Figure 51-30; individual risk scores may be calculated using any of these methods.

## OUTCOMES

### Bridge to Recovery

Not all patients with cardiogenic shock will require long-term device therapy or cardiac transplantation. For these patients, MCS can be used as a bridge until myocardial recovery can occur. The pathophysiology of cardiac remodeling following injury to the heart includes myocardial fibrosis, hypertrophy, and impaired myocyte contractility in the setting of abnormalities in neurohormonal signaling pathways. Data available from patients who have undergone device placement

**Suggested criteria for LVAD explantation**

| Authors | Suggested weaning criteria | Pump flow |
|---|---|---|
| Mancini et al. (1998)[18] | Peak $VO_2$ 20 mL/kg/min, peak CO >10 L/min | 1.6 L/min |
| Khan et al. (2003)[12] | Increase in LVEF, stable PCWP, increase in CI at maximum dobutamine | Pump off, 2 L/min |
| Dandel et al. (2005)[61] | LVEF ≥45%, LVEDD ≥55 mm | Pump off |
| Birks et al. (2006)[69] | LVEDD <60 mm, LVESD <50 mm, LVEF >45%, PCWP <12 mm Hg, CI >2.8 L/min/m², peak $VO_2$ >16 mL/kg/min, $V_E/VCO_2$ <34 | Pump off 15 min |
| Maybaum et al. (2007)[7] | Stable PCWP with reduction in flow | 2 L/min |

LVAD, left ventricular assist devices; $VO_2$, Oxygen consumption; CO, cardiac output; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; $V_E/VCO_2$, ventilatory equivalent ratio.

**FIGURE 51-31** Suggested criteria for LVAD explantation. (Reproduced with permission from Maybaum S, Kamalakanan G, Murthy S. Cardiac recovery during mechanical assist device support. *Semin Thorac Cardiovasc Surg* 2008;20:234–246.)

and eventual explant or transplant have demonstrated that many of these cellular, electrophysiological, and even neurohormonal processes can be improved and even reversed with MCS.[144] Although there are no accepted criteria for device explantation following myocardial recovery, functional studies with reduced or no device support using echocardiography and hemodynamic/metabolic parameters have been suggested by several groups when considering device explantation (Fig. 51-31).[144] The majority of data regarding successful explantation and outcomes with MCS as BTR come from patients for whom initial indication was for BTT.

The initial experience with early devices was encouraging. Among 111 patients who underwent device implantation for BTT with a mixture of both ischemic and dilated cardiomyopathy, only one patient of five experienced sustained myocardial recovery after explantation at 15 months; the remaining four patients either died or had another device implanted.[145] Nevertheless, by objective testing, half of patients with dilated cardiomyopathy and 17 percent with ischemic cardiomyopathy demonstrated at least partial myocardial recovery. Another group reported device explantation in 32 patients of 131 who underwent implantation for dilated cardiomyopathy. Among these 32 patients, 17 had sustained myocardial recovery at 3 years. Five-year survival among these patients was 78 percent.[146] In the LVAD Working Group Recovery Study, a multicenter prospective study of 67 patients with a mixture of ischemic and dilated cardiomyopathy, 6 patients met criteria and underwent explantation; 4 patients who underwent device implantation following acute heart failure enjoyed sustained myocardial recovery at 1 year, although the other two patients with chronic ischemic cardiomyopathy had clinically insignificant decreases in ejection fraction.[147]

With more modern devices, the experience has also been positive. With the HeartMate II, early experience among patients who underwent implantation as BTT reported a case of successful device explantation in one patient of 133 who underwent implantation.[58] In a subsequent report, 7 of 281 patients underwent device explantation following recovery of myocardial function at a median of 302 days (range 161–558 days).[59] Four of 43 patients reported by Frazier et al. were successfully weaned to explantation.[61] Among the European experience, 22 of 571 patients underwent explantation of the HeartMate II.[63] Use of the Jarvik 2000 as a BTR was reported in three patients who underwent explantation following 253, 407, and 683 days of support and were alive at 295, 446, and 567 days following explantation, respectively.[148] The INCOR device has been successfully explanted in 5 percent of patients in the worldwide experience of 212 patients.[81] Recovery following implantation with the DeBakey VAD has also been reported.[50]

One approach to BTR has been described using LVAD therapy for patients with dilated cardiomyopathy combined with maximum medical support including clenbuterol, a novel selective $B_2$ agonist (Harefield protocol).[149,150] Of 24 patients in the study, 11 patients underwent explantation after a median period of 388 days. Nine of these patients survived (one died postoperatively and one succumbed to cancer), and of the surviving patients, 100 percent were free from heart failure at 1 year and 89 percent at 4 years.[151] With this therapy, 46 percent of patients underwent successful explantation, compared with only 13 percent in the LVAD Working Group study. Currently, this protocol is being examined in an ongoing, multicenter clinical trial. The Harefield Recovery Protocol Study (HARPS) is a combination of maximal medical heart failure therapy along with device support and clenbuterol.

Future identification of patients who are most likely to have sustained myocardial recovery following device explantation and development of maximal adjunctive medical therapies will hopefully increase the number of patients who will benefit from MCS as a bridge to myocardial recovery.

## Bridge to Transplant

MCS has been most commonly used as a method in patients whose native heart function is not expected to recover, but who can benefit from medical optimization prior to undergoing heart transplantation. Currently the most common

indication for device implantation, both early and modern devices have demonstrated success for this indication.

Among the early devices, Frazier et al. demonstrated a benefit among transplantation candidates who received MCS as BTT therapy.[39] In this study, patients who were refractory to maximal medical support (inotropes with or without intra-aortic balloon counterpulsation) who underwent implantation of the HeartMate VE LVAD were compared to historical patients who received maximal medical support without device implantation. Following initiation of MCS, renal and hepatic function were significantly improved from predevice levels. Both survival prior to transplantation (71 vs 33 percent) as well as 1-year survival after transplantation (84 vs 63 percent) was significantly improved among patients who underwent BTT therapy compared to medical support alone. Further studies confirmed a benefit in survival to transplantation, but have differed with regard to potential benefit posttransplantation. One study showed no difference in survival, and two actually showed reduced survival; the impact of VAD on the pre-and posttransplant recipient may not be fully understood in the absence of a prospective, randomly controlled trial among patients awaiting cardiac transplantation.[152–154] One potential explanation for the differences in posttransplant survival may have to do with patient selection. Patients with more severe heart failure decompensation refractory to medical intervention have been shown to have worse outcomes with up to three times the mortality in the pretransplant period compared to those patients with less severe myocardial dysfunction and those with response to medical heart failure therapies.[155]

Recent trials with newer-generation devices have also shown a benefit from MCS prior to transplantation. Miller et al. reported a clinical trial of the HeartMate II device among 133 patients with end stage heart disease awaiting cardiac transplantation.[58] The main outcome of this trial was successful transplantation, continued support, or cardiac recovery at 180 days. Seventy five percent of patients reached this endpoint, including 56 who proceeded to transplantation and 43 who remained active on the transplant list. Overall survival was 75 percent at 6 months and 68 percent at 1 year. A follow-up study that reported on 281 of the 469 patients who underwent HeartMate II implantation while awaiting cardiac transplantation also showed excellent results at 18-month follow-up.[59] During this time period, 79 percent of patients underwent transplantation or had continued device support. Survival at 18 months was 72 percent. Lahpor reported the European experience with the HeartMate II as BTT and of 571 patients; 23 percent underwent transplantation and 42 percent had ongoing support at 6 months.[63] Lorforte reported a 50 percent transplantation rate, including18 patients who were supported for a mean of 217 days and achieved posttransplant survival rate of 66.6 percent.[64,77]

Goldstein reported the international experience with the DeBakey VAD implanted in 150 patients for BTT.[50] Among these patients, there was a cumulative support time of 30.4 patient years, with 55 percent proceeding to transplantation (62 patients) and 19 patients remaining on the active transplant list (19 patients). The longest support time was 492 days, and 13 percent of patients were on support for greater than 6 months.

Initial reports of the Jarvik 2000 in 22 patients were also good; 13 patients proceeded to transplantation and another two were active on the waiting list with an average support time of 67 days.[54] In another group, 22 patients who received the Jarvik 2000 were supported for a mean of 280 days with 7 patients receiving a heart transplant, 4 remaining on the list, and 3 with myocardial recovery.[148] Siegenthaler reported on 83 patients who underwent implantation of the Jarvik 2000, with a mean support time of 159 days and a maximal support time of 2.7 years.[55]

Wieselthaler reported the first experience with the Heartware device in 23 patients who achieved a mean support time of 167 days.[73] By the 180-day endpoint, 2 patients underwent transplant and 19 patients continued support for longer than 6 months with 6- and 12-month survivals of 91 and 86 percent. The ADVANCE study reported the BTT experience among 140 patients and compared them to patients who underwent implantation of other commercially available devices during the same time period.[79] The survival was 92 and 91 percent at 1 year, which were comparable to the alternative devices.

The use of the VentrAssist device as BTT was promising among the 400 patients who were implanted with this device; 36 to 40 percent of patients underwent transplantation and 42 to 44 percent had continued support, but due to technical and financial difficulties this device was ultimately discontinued.[68,69]

The Syncardia (CardioWest) TAH has also shown good results as BTT therapy. Among the 81 patients in a clinical trial, 79 percent of patients went on to successful transplantation with 1- and 5-year survivals for patients who underwent transplantation of 86 and 64 percent, respectively.[85] When compared to the control arm (no MCS), both survival to transplantation and survival posttransplant were improved.[85] Another experience with 127 patientsreported up to 74 percent of patients who successfully proceeded to transplantation.[86]

BTT has been reported to be successful with the INCOR device; 31 percent of patients were successfully bridged to transplant and another 20 percent remained active on the list out of the 212 patients who underwent implantation worldwide.[81]

Although these data are promising, determination of the optimal patient, device, and timing of implantation will be crucial to ensure the best outcomes among these patients.

## Destination Therapy

MCS is often considered as DT for patients with severe, end stage heart failure who are not expected to recover native myocardial function and who are not candidates for cardiac transplantation. Several landmark clinical trials of MCS for DT using early devices are of historic interest and established

**Patient chararcteristics and survival outcomes of DT**

| Clinical trials of DT | REMATCH | | CUBS | INTREPID | Post-REMATCH |
|---|---|---|---|---|---|
| LVAD tested | Medical therapy | HeartMate VE | LionHeart | Novacor | HeartMate XVE |
| Number of patients | 61 | 68 | 23 | 37 | 309 |
| Years of enrollment | 1998–2001 | 1998–2001 | 1999–2004 | 2000–2003 | 2002–2005 |
| Mean age (y) | 68 ± 8 | 66 ± 9 | 65 ± 4.3 | 60 ± 11.2 | 60.7 ± 12 |
| Cardiac index (L/min/m²) | 2 ± 0.6 | 1.9 ± 1 | 1.7 ± 0.4 | Not available | 2.1 ± 0.7 |
| Left-ventricular ejection fraction (%) | 17 ± 4.5 | 17 ± 5.2 | 22 ± 5 | 14.2 ± 4 | 17.6 ± 6 |
| Ischemic cardiomyopathy (%) | 69% | 78% | 61% | 57% | 65% |
| Long-term outcomes | | | | | |
| % 1-year survival | 25% | 52% | 39% | 27% | 56% |
| % 2-year survival | 8% | 23% | 22% | 20% | 31% |
| Fatal device failure | None | 7 | None | None | 10 |

DT, destination therapy; REMATCH, Randomized Evaluation of Medical Assistance in the Treatment of Congestive Heart Failure; CUBS, Clinical Utility Baseline Study; INTREPID, Investigating of the Non-Transplant Eligible Patients who are Inotrope Dependent; LVAD, left ventricular assist device.

**FIGURE 51-32** Published results from clinical trials of mechanical circulatory support for DT. (Reproduced with permission from Lietz K, Miller LW. Destination therapy: Current results and future promises. *Semin Thorac Cardiovasc Surg* 2008;20:225–233.)

this use for MCS (Fig. 51-32).[156] Newer studies using modern devices have also been published and further strengthened this application for device therapy.

The landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial was the first to compare survival with MCS with the HeartMate VE LVAD to that of optimal medical management.[136] It demonstrated improved survival in patients supported with LVADs compared to medical management alone (1-year survival: 52 vs 25 percent, 2-year survival: 23 vs 8 percent, respectively) and validated the use of these devices for long-term support in patients who were not candidates for transplantation. A follow-up study, the post-REMATCH group, compared patients who received the newer HeartMate XVE LVAD and again demonstrated an increase in 1- and 2-year survivals of 56 and 31 percent compared to their control group of 25 and 8 percent (Fig. 51-33).[157]

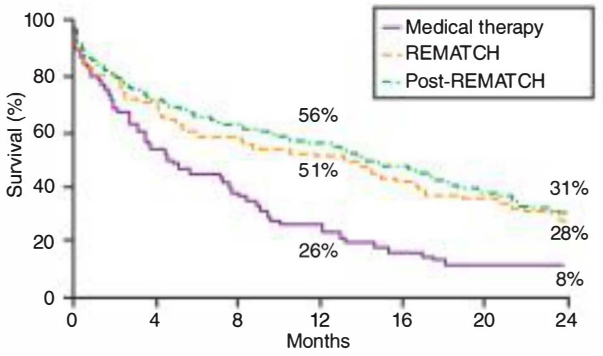



**FIGURE 51-33** Survival of patients undergoing DT in the REMATCH and post-REMATCH groups compared to medical therapy alone. (Reproduced with permission from Lietz K, Miller LW. Destination therapy: Current results and future promises. *Semin Thorac Cardiovasc Surg* 2008;20:225–233.)

Following the REMATCH trial, results of the Investigation of Nontransplant-eligible Patients Who Are Inotrope Dependent (INTrEPID) trial were published.[158] This trial included patients who had all failed inotropic management, and compared those who received LVAD therapy with a Novacor device to those patients who elected not to receive an LVAD device. Despite the fact that this cohort of patients was even sicker than those in the REMATCH trial, there was a significant improvement in survival with LVAD therapy compared to medical therapy alone (6-month survival: 46 vs 22 percent, 12-month survival: 27 vs 11 percent, respectively.

The lessons from REMATCH demonstrated that there is a cohort of patients who benefit from LVAD support over medical therapies. These include inotrope-intolerant patients (e.g., ventricular arrhythmias), patients requiring complex and/or multistage operations, patients with life-threatening coronary lesions not amenable for coronary revascularization, and patients with severe end-stage heart failure. These risks must be balanced with the survival benefit provided by mechanical support. Hence, it is important to identify high-risk candidates who might be optimized prior to device implantation to avoid associated morbidity and mortality.[136]

A European trial, the CUBS trial reported an experience with the LionHeart 2000 ventricular assist system.[159] The survival from this trial was not as good as previously published trials; however, the patients in this trial were generally sicker than those included in the device implant group for the landmark REMATCH trial or later studies. Survival at 1 and 2 years following initiation of MCS for DT were 39 and 22 percent, respectively.

The first trial to compare two different devices for DT was a multicenter clinical trial in which 200 patients who were not eligible for transplant were randomized to receive either a pulsatile HeartMate XVE or nonpulsatile HeartMate

II for DT.[60] The results of this trial demonstrated that the HeartMate II group achieved superior outcomes comparedto the HeartMate XVE group in terms of stroke, reoperation free survival (46 vs 11 percent), and overall survival (58 vs 24 percent) at 2 years. In addition, adverse events (device replacement, infection, right heart failure, arrhythmia, respiratory failure, and renal failure) were less common with the HeartMate II device compared to the HeartMate XVE. This multicenter trial supported the use of the HeartMate II as DT for end stage heart failure. Other studies that support this indication came from Frazier et al., who reported 17 patients with a longest support time of over 700 days, Lahpor et al. who reported 119 patients with a mean duration of support of 236 days, and Granfeldt et al. who reported a patient with over 3 years of support.[61,63,160]

Other devices have also shown to be useful as DT. Siegenthaler reported successful use of the Jarvik 2000 as DT in 19 patients with a mean support time of 445 days and maximal support time of 4.9 years.[55] The longest surviving patient with the Jarvik 2000 has been alive for over 6 years.[53] Among the 14 AbioMed TAH implants, the majority were alive 2 months following implantation with the longest survivor living formore than 1 year.[88,89] Prior to its removal from the marketplace, the VentrAssist device also showed success for DT; among 16 patients who received a device as DT, 1- and 2-year survivals were 80 and 60 percent, respectively.[68] The Heartware device is currently being investigated in the ENDURANCE trial as DT.

## SUMMARY

MCS is used in patients whose heart failure cannot be ameliorated with medical management alone. Devices have evolved from early paracorporeal pulsatile devicesto modern intracorporeal pulseless axial flow models and even TAHs capable of biventricular support. Indications for clinical use include BTR for patients in whom myocardial recovery is anticipated, BTT prior to cardiac transplantation, and DT for patients who have contraindications to transplantation.

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## MECHANICAL CIRCULATORY SUPPORT BOARD REVIEW QUESTIONS (CHAPTER 51)

1. Which is not a currently accepted use for mechanical circulatory support?
   A. As a method to optimize tissue perfusion and maintain adequate cardiac output while awaiting definitive cardiac transplantation (bridge to transplant)
   B. As lifelong permanent therapy for refractory end-stage heart failure (destination therapy)
   C. As temporary support to unload the heart and allow myocardial recovery from a potentially reversible insult (bridge to recovery)
   D. As temporary support while determining other organ suitability for transplant (bridge to donation)
   E. As temporary support prior to determination of candidacy for permanent mechanical circulatory support (bridge to bridge)

2. Which of the following is a contraindication to mechanical circulatory support?
   A. Need for both right and left heart support
   B. Dialysis-dependent renal failure
   C. Moderate aortic insufficiency
   D. Atrial fibrillation
   E. Patent foramen ovale

3. Which of the following is true regarding permanent mechanical circulatory devices?
   A. Device placement usually is performed on cardiopulmonary bypass.
   B. The inflow cannula is typically inserted into the right superior pulmonary vein and the outflow cannula in the aortic arch.
   C. Postoperative anticoagulation with Coumadin is optional for most devices.
   D. The device is positioned within the peritoneum.
   E. The drive line should be tunneled out through the left lower quadrant.

4. During LVAD implantation, which echocardiographic plane is best for assessing the mitral valve?
   A. Axial
   B. Coronal
   C. Double-oblique
   D. Vertical long axis
   E. Short axis

5. Which of the following is correct regarding device-specific complications of mechanical circulatory support?
   A. Transfusion is required in less than 50 percent of patients.
   B. Suppressive long-term antibiotics are necessary to reduce infection.
   C. Thromboembolism is the most common complication.
   D. Overall infection rates are about 30 percent.
   E. Postimplant organ failure occurs in less than 10 percent.

## ANSWERS

1. **Answer: D.** There is no indication for implantation of mechanical circulatory support in order to maintain an individual for possible organ donation. Current indications for mechanical circulatory support include bridging temporary devices to more permanent devices, bridge to transplantation, bridge to recovery, and destination therapy.
2. **Answer: B.** Patients with renal failure are not candidates for mechanical circulatory support. Biventricular failure is an indication for mechanical support. Moderate aortic insufficiency and patent foramen ovale should both be corrected at the time of initiation of circulatory support. Atrial fibrillation and other dysrhythmias should be aggressively treated, but are not contraindications to mechanical support.
3. **Answer: A.** Placement of a permanent LVAD usually required cardiopulmonary bypass for insertion of the uptake cannula into the left ventricular apex. Insertion of the uptake cannula into the right superior pulmonary vein is performed for temporary LVAD placement. Postoperative anticoagulation with Coumadin is the rule for most devices. The devices should ideally be placed in a preperitoneal pocket to avoid injury to intra-abdominal organs. The drive line exits the skin in the right upper quadrant.
4. **Answer: D.** The vertical long axis view provides the optimal plane for mitral valve evaluation. The axial plane is best for the overall heart view and extracardiac structures. The coronal plane visualizes the left ventricular outflow tract and aortic valve. The double-oblique plane is best for the arch and evaluation of dissection. The short-axis plane is best for assessing wall motion abnormalities.
5. **Answer: D.** Meticulous sterile technique and improvements in implantation procedures has reduced overall infection rates to about 30 percent. Transfusion of any blood product is necessary in over 75 percent of patients. Suppressive long-term antibiotics are not indicated after device implantation. Bleeding, not thromboembolism, is the most common complication. Postimplant organ failure occurs in 10 to 30 percent of patients.

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# 52 Surgical Ventricular Remodeling

*Clinton D. Kemp*
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**KEY CONCEPTS**

- Epidemiology
  - Congestive heart failure (CHF) is the most prevalent medical problem in Western society as the leading cause of death in the United States. Ischemic cardiomyopathy (ICM) is the leading cause of CHF, affecting 75 percent of patients with CHF.
- Pathophysiology
  - ICM is generally caused by a full-thickness myocardial infarction (MI), followed by ventricular remodeling. This remodeling process can result in progressive dilation of the ventricle, leading to an increase in the end-diastolic diameter and volume, an increase in left ventricular wall stress and oxygen demand, a loss of the left ventricle's natural elliptical shape with the development of a more rounded form, the development of mitral insufficiency and, ultimately, a worsening of global systolic function.
- Clinical features
  - Progressive CHF due to ICM results in debilitating congestive symptoms, including dyspnea, fatigue, peripheral edema and, in its end stages, acute and/or chronic multisystem organ failure. Classically, patients are candidates for surgical ventricular remodeling (SVR) if they have had an anterior MI, have a large area of akinesis or dyskinesis, and have clinical evidence of CHF.
- Diagnostics
  - Preoperative diagnostics include cardiac catheterization with coronary angiography. Other potentially useful diagnostics include myocardial viability and magnetic resonance imaging studies.
- Treatment
  - The surgical goals of SVR include complete revascularization of all viable territories, exclusion of akinetic and dyskinetic segments with a concomitant reduction in the size of the nonfunctioning anteroseptal portion of the heart, recreation of the elliptical shape of the heart, and repair of any valvular incompetence by valve repair or replacement.
- Outcomes/prognosis
  - SVR has been shown to improve ventricular size, morphology, left ventricular ejection fraction (EF), stroke-volume index, endocrine markers of CHF, ventricular energetics, ventricular synchrony, and mechanical efficiency. Clinically, it results in improved functional capacity (New York Heart Association class) and an excellent 5-year survival in very sick patients. Further study and experience are needed to optimize patient selection and timing for surgical intervention as well as to better define the mechanistic basis behind the beneficial effects of SVR.

## INTRODUCTION

Congestive heart failure (CHF) is a major medical problem facing Western society today. It is the leading cause of death in the United States, representing over one-quarter of all deaths and is expected to become even more significant in the years ahead.[1] The incidence of new CHF cases are on the rise as more than 400,000 new cases per year continue to add to the over 5 million people living with CHF in the United States.[1] Ischemic cardiomyopathy (ICM) is the leading cause of CHF, affecting some 75 percent of patients with this condition.[2,3] Medical and surgical therapies have been shown to be effective in improving survival and quality of life in CHF patients.[4] Coronary artery bypass grafting (CABG) has been shown to be effective in some patients with ICM, but heart transplantation and left ventricular assist devices are more effective in patients with advanced heart failure.[5] Surgical ventricular remodeling (SVR) is a surgical procedure whose

roots arise from the surgical treatment of left ventricular aneurysms. Also known as surgical ventricular restoration, endoventricular circular patch plasty, and the Dor procedure, SVR has been shown to be an effective treatment for select patients with ICM. In this chapter we will review the pathophysiological basis and the clinical experience with SVR.

## PATHOPHYSIOLOGY

The pathophysiology of ICM is related to the changes that occur following full-thickness myocardial infarction (MI). Following infarction, the left ventricle (LV) undergoes a well-described process of ventricular remodeling.[6] Left unchecked, this process can lead to a progressive dilation of the ventricle, resulting in an increase in the end-diastolic diameter and volume, an increase in LV wall stress and oxygen demand, a loss of the ventricle's natural elliptical shape with the development of a more rounded contour, the development of mitral insufficiency and, ultimately a worsening of global systolic function.[6,7] The development of mitral regurgitation is due to factors specific to ventricular remodeling as well as unrelated leaflet issues. They include annular dilation due to global ventricular enlargement, restricted leaflet motion and reduced coaptation due to leaflet tethering, or involvement of the papillary muscles with the infarction. These factors combine to prevent or limit leaflet coaptation in the proper plane, resulting in central regurgitation. Superimposed leaflet pathology can worsen the functional regurgitation.

Postinfarction dysfunction is further affected by both the electrical and mechanical dyssynchrony that develops following infarction.[8] The concept of electrical dyssynchrony suggests that abnormalities in the conduction system following infarction result in differential timing of left and right ventricular contraction. This dyssynchronous contraction results in diminished overall LV function, a condition treated, in appropriate circumstances, with biventricular pacing. Mechanical dyssynchrony is a phenomenon of impaired LV function caused by nonuniform contraction, relaxation, and filling of the ventricle due to juxtaposed areas of akinesis, dyskinesis, and hypokinesis alongside normal areas. This has been associated with reduced survival.[8,9]

The prognosis of patients with ICM is related to the size of the LV and the impact that remodeling has had on the function of the remote noninfarcted zones.[7,10,11] Infarction results in a disruption of the normal spiral arrangement of myocardial fibers.[12] The normal spiral architecture helps to resist deformation, direct blood flow toward the aortic valve, and optimize contractile efficiency. Loss of this architecture leads to a more spherical ventricle. Loss of an elliptical shape leads to a progressive reduction in contractile force, ultimately leading to death.[8,9] Since the seminal work of White, studies ranging from GUSTO to STICH have all shown that LV size is a surrogate marker of mortality in CHF.[10,12]

Coronary artery revascularization, details of which are presented elsewhere in this book, has been shown to improve survival in both normal and abnormal ventricles.[5] Improved blood flow, however, cannot improve the function of the scarred, noncontractile areas of the heart, reduce dyssynchrony, or reverse the morphological changes of infarction. Surgical techniques have been developed to arrest the progression and reverse the morphologic changes induced by the pathologic process of postinfarction ventricular remodeling. Such techniques are commonly referred to as SVR. SVR is not one techniquebut several, all of which have the same surgical goals: to reduce the size of the LV and restore a more normal elliptical shape to these enlarged spherical hearts to improve cardiac function. SVR is often performed in conjunction with coronary artery revascularization and mitral valve repair/replacement. In this chapter, these techniques are presented and the clinical outcomes discussed.

## HISTORY

The history of the surgical approach to postinfarction remodeling begins with the approach to postinfarction LV aneurysms. Denton Cooley was the first to attempt to change the shape of the ventricle when he performed the first linear LV aneurysmectomy on cardiopulmonary bypass (CPB) to treat a calcified LV aneurysm in 1958.[13]

Many other techniques and approaches were developed over the years to treat postinfarction ventricular aneurysms.[14] Fontan originally described the use of endoventricular purse-string sutures to reduce the size and reapproximate the wall of the LV.[15] Jatene developed a technique of septoplasty and modified linear closure in the early 1980s.[16] At the same time, Vincent Dor and colleagues introduced the technique of endoventricular circular patch plasty, which later, in 1985, came to bear his name.[17] His approach was unique in that it approached akinetic areas and dyskinetic aneurysms equally. He later began to apply this technique to treat CHF and altered the way in which changes in ventricular morphology are approached. Cooley and colleagues later utilized a similar technique for aneurysmal resection by patching the anterior wall from within the ventricle but without the encircling purse-string suture to reduce the volume of the anterior wall of the LV.[18]

The concept of reconstructing the ventricle to a prescribed size based on the patient's body size was introduced by Dor and popularized by Menicanti.[19] The best methodology to determine the appropriate size of the reconstructed ventricle has yet to be determined. Some surgeons base it on the enlarged end-diastolic dimensions and others by indexed body surface area.[19] Additional technical approaches that merit mention include a linear closure and septoplasty approach described by Mickleborough, a modified linear closure technique popularized by Guilmet in which there is direct endoventricular apposition of the lateral wall to the septum to create a new anterior wall, and a concentric purse-string or "cerclage" technique followed by linear closure

**TABLE 52-1: Indications for Surgical Ventricular Remodeling**

| |
|---|
| **Anteroseptal myocardial infarction** |
| NYHA class 3 or 4 congestive heart failure |
| Retained basilar heart function |
| Depressed ejection fraction (%) |
| Large area of akinesis/dyskinesis |
| Asynergy of >35% of left ventricle |
| **Enlarged ventricle** |
| End-diastolic volume index >120 mL/m² |
| End-systolic volume index >60 mL/m² |
| Candidate for valve repair/replacement |
| Candidate for revascularization |
| Good right ventricular function |

utilized by McCarthy.[20,21] The end result of two decades of surgical innovation are four techniques used for ventricular remodeling procedures today.

## INDICATIONS FOR SURGERY

Classically, patients are candidates for SVR if they have had an anterior MI, have a large area of akinesis or dyskinesis, and have clinical evidence of CHF. Specific characteristics of patients who have successfully undergone SVR are shown in Table 52-1. Ideal candidates have akinesis/dyskinesis in the anteroseptal area, have retained function of the basilar and lateral portions of the heart, and have good right ventricular function. They should also be candidates for revascularization and mitral valve repair if needed. Included in many clinical series of SVR are patients who have had anterior infarctions with areas of akinesis or dyskinesis with lesser degrees of ventricular enlargement and CHF. The indication for surgery in these patients is angina in other territories with the need for coronary artery revascularization. In such patients, the goal of therapy is to prevent dilation and the clinical development of CHF, which is an inevitable part of postinfarction remodeling. Relative contraindications are shown in Table 52-2. Many patients have additional cardiac conditions that will necessitate repair or replacement, and they should be candidates for surgical repair of any lesion that exists. Success has also been demonstrated in groups of patients with more complex pathologies such as multiterritory infarctions, truly advanced end-stage CHF, and the need for multiple concomitant procedures.[22,23]

**TABLE 52-2: Relative Contraindications to Surgical Ventricular Remodeling**

| |
|---|
| Multiple areas of infarction |
| Loss of basilar myocardial function |
| Pulmonary hypertension and right ventricular dysfunction |
| Unreconstructable coronary artery disease |

## SURGICAL APPROACHES

The surgical goals of SVR include complete revascularization of all viable territories, exclusion of akinetic and dyskinetic segments with a concomitant reduction in the size of the nonfunctioning anteroseptal portion of the heart, recreation of the elliptical shape of the heart, and repair of any valvular incompetence by valve repair or replacement.

## SURGICAL TECHNIQUE

Several different surgical approaches are used to achieve the goals stated above. Common among each of the approaches is the median sternotomy incision, which is standard in cardiac surgery. The surgical procedure begins with standard arterial and venous cannulation for CPB. If mitral valve repair or replacement is a strong possibility, cannulation of both the inferior and superior venae cavae is recommended. The LV can be vented directly through its apex, through the left atrium via the right superior pulmonary vein, or through the aortic root. Prior to systemic heparinization, femoral arterial access is obtained to make the later placement of an intra-aortic balloon pump easier if necessary. Since concomitant CABG is usually performed, a standard approach for CABG is utilized, including myocardial protection.

Once the patient is on CPB, the sequence of procedures performed is a matter of personal preference. Most commonly, CABG is performed first. Once this is accomplished, the SVR or mitral valve replacement (MVR) can be performed next.

The mitral repair can be done utilizing any technique preferred. An intraventricular repair as described by Menicanti is done through the ventriculotomy prior to performing the SVR.[19] Our standard approach is to perform a reduction posterior annuloplasty through a standard interatrial groove incision prior to performing the SVR to avoid the remote possibility of disrupting our ventricular closure.

In the arrested heart with the LV vented, the LV will often collapse, demonstrating the area of thinned-out scar. If this does not happen, it may be due to a partial-thickness infarction. The absence of collapse does not contraindicate SVR and simply means that revascularization occurred early enough to prevent full-thickness infarction.

The technique employed at Hopkins is a variation of the endoventricular circular patch plasty popularized by Vincent Dor. It is depicted in Figures 52-1 to 52-7. An incision is made into the anterior wall of the LV through the area of scar. In a typical anterior infarction, the incision is extended distally to the apex and proximally parallel to the course of the left anterior descending coronary artery until normal muscle is encountered. Retention sutures are placed into scar to aid in achieving and maintaining exposure.

The ventricle is inspected and any thrombus is removed. During inspection of the ventricle, the extent as well as the transmurality of the scar is noted. A transition zone between infarcted and noninfarcted muscle is often palpable. This

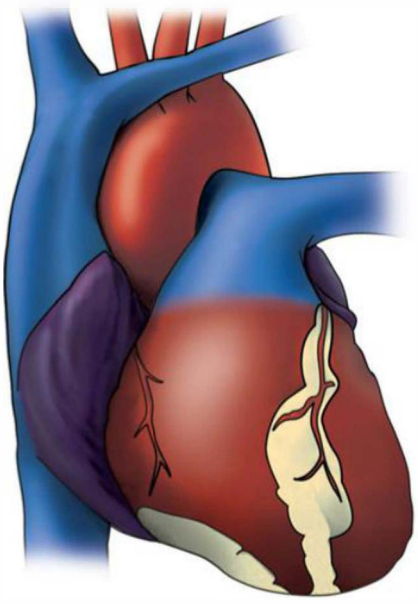


FIGURE 52-1 Normal heart.

is particularly evident with full-thickness infarctions but is notably absent in some patients who have received thrombolytics or percutaneous revascularization prior to widespread cell death. These patients may demonstrate a mosaic pattern of ventricular scarring. Such ventricles often show akinesis rather than dyskinesis. The presence or absence of a clear

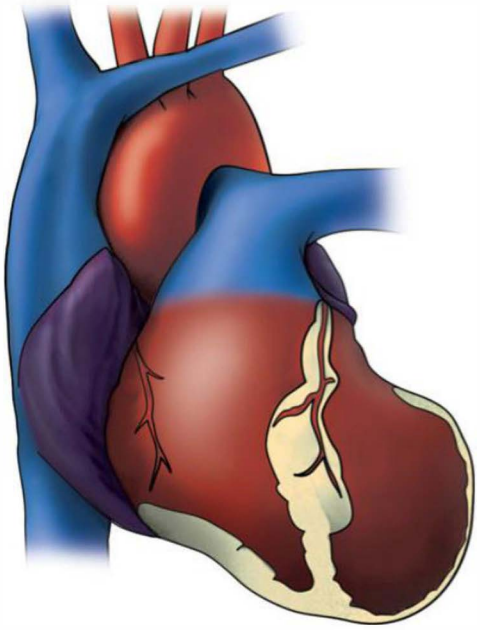


FIGURE 52-2 Heart with thinned akinetic ventricle following anterior wall myocardial infarction.

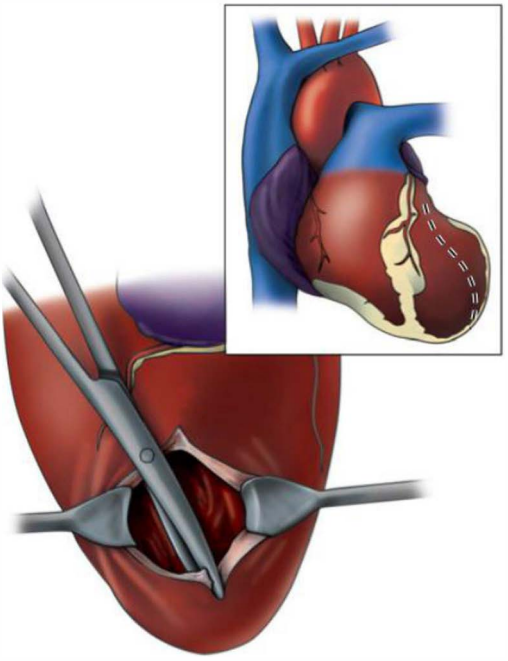


FIGURE 52-3 Anterior ventriculotomy parallel to the course of the left anterior descending coronary artery.

transition zone is not known to be of clinical significance. The differences in the various operations are apparent from this point forward in the operation.

At this point in the procedure with many techniques, an encircling purse string of 2-0 polypropylene suture is placed along the anterior border of the sizing device. Placement of the purse-string, often called the "Fontan stitch," is one of the key steps in the operation. It chooses the new apex of the heart and defines the outline of the new anterior wall. Selecting the location of the purse strings is usually done by personal preference. It can be done in a measured fashion, using one of several commercially available sizing devices, by selecting a site based on experience or proximity to a landmark such as the papillary muscles, or at the border of infarcted and noninfarcted tissue. Use of the "border zone" was most commonly recommended before the development of commercially available devices. If a sizing device is used, a variety of methods of determining the size of the device to be used have been recommended (Fig. 52-4). Our device is selected based on a volume of 50 to 60 mL/m$^2$ body surface area. Obese patients will have the volume titrated down slightly and cachectic patients will have it titrated up.

Once the anterior wall is encircled with the purse-string suture, it is reconstructed utilizing a variety of techniques. It is important to place the purse-string in such a fashion as to create an elliptical ventricle (Fig. 52-5). A patch of Dacron is used if the remaining defect is greater than 2 to 3 cm long. An oval patch is cut to the appropriate size and sutured in place, closing the defect. Care is taken to place the patch sutures around the anterior purse string. The patch may be

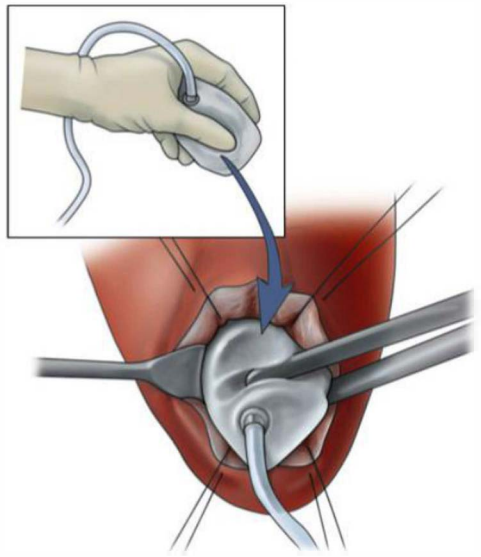


FIGURE 52-4 Insertion of ventricular sizing device following placement of retention sutures for exposure. The volume of the sizing device is selected on the basis of body surface area (50–60 mL/m²).

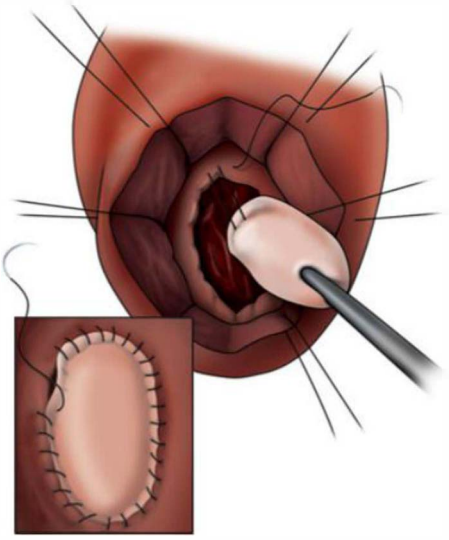


FIGURE 52-6 Patch closure reconstruction of anterior wall for residual ventriculotomy openings of greater than 3 cm. Smaller residual defects are closed primarily.

sutured using a continuous or interrupted technique. Prior to completing the patch, the left ventricular vent is shut off, allowing the ventricle to fill with blood and forcing air to escape the ventricle through the partially completed closure (Fig. 52-6). After the patch is sutured into place, a linear closure is performed superficial to the patch or purse-string. Horizontal mattress sutures, buttressed with bovine pericardium, are used as a first layer of closure. The second layer is a continuous running stitch of 2-0 polypropylene (Fig. 52-7). If the defect is moderate in size but not large enough for

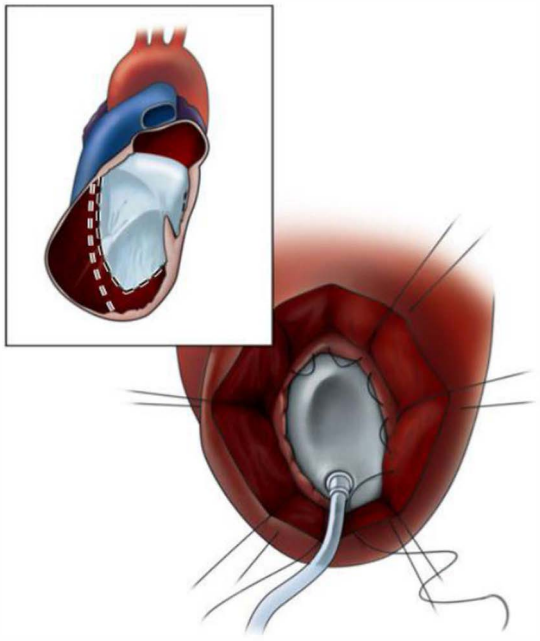


FIGURE 52-5 Placement of purse-string suture to define margins of reconstruction of anterior wall.

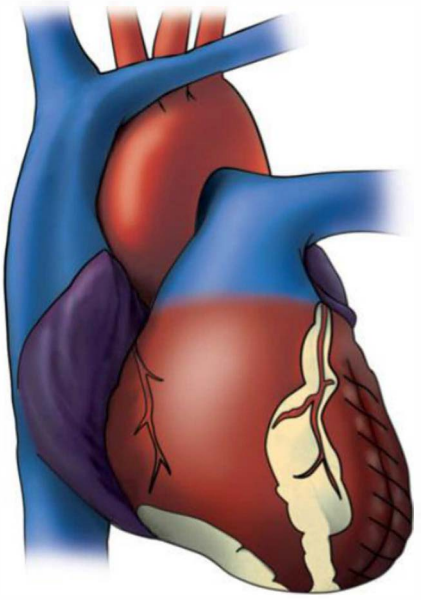


FIGURE 52-7 Two-layer closure of ventriculotomy. Horizontal mattress sutures are used for the first layer, followed by continuous running suture for the second layer.

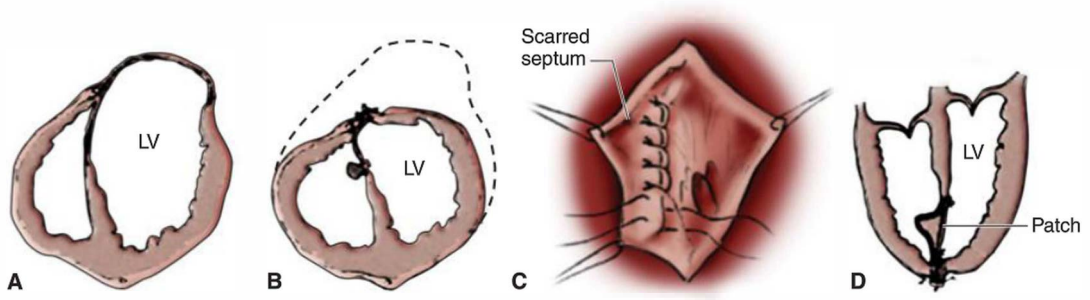



**FIGURE 52-8** Linear closure of Guilmet. The deep scar of the septum is sewn directly to the deep scar of the lateral wall internally. (Adapted from Mukaddirov M, Demaria RG, Perrault LP, et al. Reconstructive surgery of postinfarction left v entricular aneurysms: Techniques and unsolved problems. *Eur J Cardiothorac Surg* 2008;34:256–261. Copyright Elsevier.)

patching, the ventricle can be reapproximated superficial to the purse-string using a linear closure, usually reinforced.

An alternative technique advocated by Linda Mickleborough employs a modified linear closure and patch septoplastyto accomplish the same SVR surgical goals. This technique uses the same anterior ventriculotomy approach to expose the septum and anterior wall. This technique employs a more traditional linear closure to exclude the akinetic or dyskinetic areas of the anterior wall. In addition, the dilated, fibrotic areas of the infarcted septum are addressed by either including the septum in the linear closure of the anterior wall or patching the septum and including the patch in the linear closure.[24]

A technique of multiple purse strings is employed by Pat McCarthy. Also called the cerclage technique, it begins as the previous two techniques. Once the anterior wall purse string is placed and tied, additional purse strings are placed a few millimeters superficial to the previous purse string. This continues anteriorly until the final remaining defect is small and is closed with a standard linear closure.[25]

A modified septoplasty technique, employed by Jatene, aimed to reduce the volume of the infarcted septum in conjunction with a patch or primary closure. This technique also begins in the same way as other SVR procedures. An anterior encircling purse-string is placed to define the borders of the anterior wall, as is done in some of the other SVR techniques. The distinguishing characteristic of this technique is the placement of mattress sutures in the septum to reduce the horizontal length of the septum. Once the septal reduction is performed, the anterior encircling purse-string is tied and the anterior wall closed primarily or with a patch.[16]

A final technique utilizes an internal linear closure described by Guilmet.[26] With this technique, the deep scar of the septum is directly sewn to the deep scar of the lateral wall internally. This excludes the more superficial scar and aligns the remaining septal and lateral scar tissue for a linear closure (Fig. 52-8).

A word should be mentioned about performing the SVR with the heart beating. One advantage is that poorly functioning, often ischemic ventricles are not further injured during the period of cardiac arrest. Another is that the degree of mitral regurgitation and the result of mitral repair can be assessed in a beating heart, which is felt by some to be advantageous. A final advantage is that it allows the border between contracting and noncontracting segments of the heart to be seen more clearly from within the ventricle, which may aid in performing the SVR. The disadvantage is that it is much more difficult to place the sizing device on the mitral annulus and keep it there to allow accurate placement of sutures. This disadvantage can be partially compensated for by tracing the outline of the margins of the sizer on the endocardium and then deflating the sizer. In retrospective studies, SVR performed on the beating heart or with cardioplegic arrest has demonstrated no differences in outcomes. However, the novice may be aided with cardiac arrest until experience is gained. D'Onofrio reported a retrospective review of 588 patients who underwent SVR with normothermic CPB and a beating heart or with hypothermic CPB and cardioplegic arrest and found no difference in outcome with regard to LV volume reduction, ejection fraction (EF), improvement NYHA class, 30-day mortality, or long-term mortality between the groups.[27] An analysis of the 1188 patients in the RESTORE (Reconstructive Endoventricular Surgery Torsion Original Radius Elliptical) group also showed no difference in outcomes when patients who underwent beating heart SVR were compared to those who underwent hypothermic CPB and cardioplegic arrest.[28]

## PHYSIOLOGICAL CHANGES AFTER SURGICAL VENTRICULAR REMODELING

The goal of SVR is to recreate a normal-sized ventricle from the remaining functional myocardium while at the same time eliminating akinetic or dyskinetic segments. Several groups have reported physiological data from patients who have undergone SVR in order to better understand the post-SVR physiology.[29–43] Preoperatively, those with MR have more severe physiological dysfunction, with larger areas of

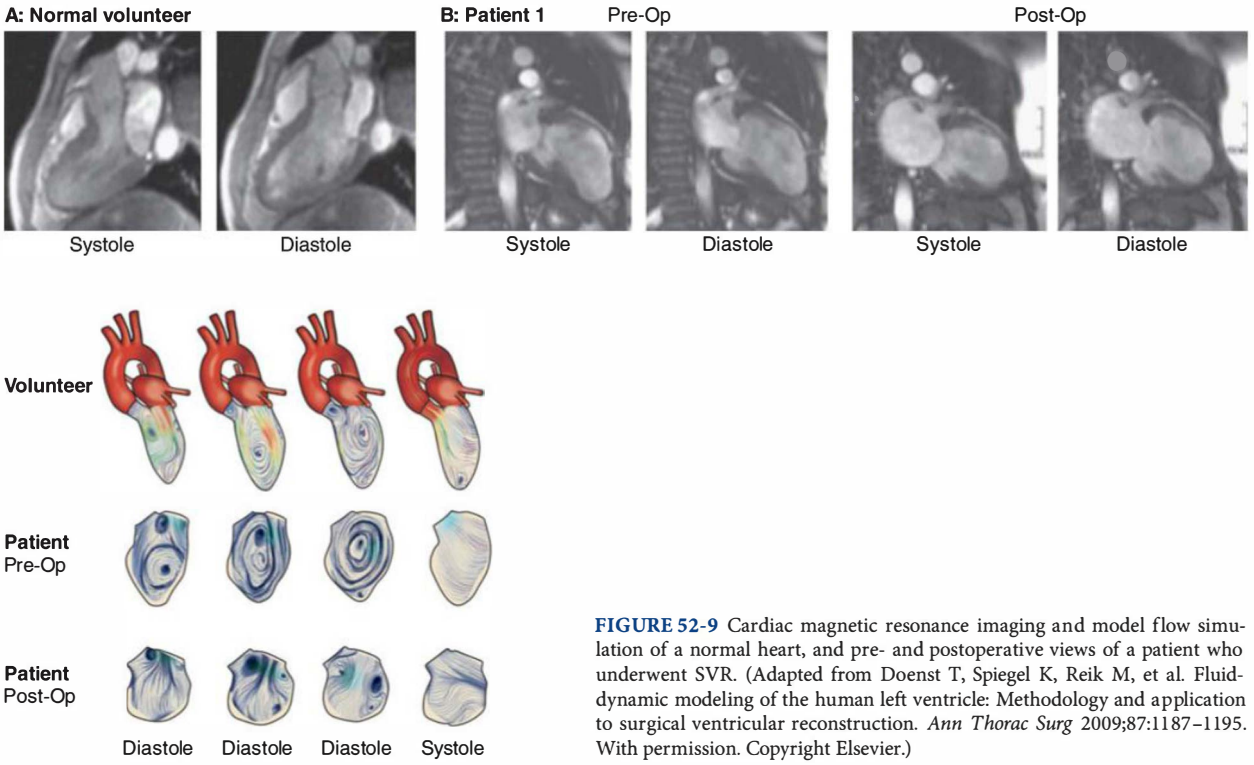



**FIGURE 52-9** Cardiac magnetic resonance imaging and model flow simulation of a normal heart, and pre- and postoperative views of a patient who underwent SVR. (Adapted from Doenst T, Spiegel K, Reik M, et al. Fluid-dynamic modeling of the human left ventricle: Methodology and application to surgical ventricular reconstruction. *Ann Thorac Surg* 2009;87:1187–1195. With permission. Copyright Elsevier.)

akinesia, greater LV volumes, and lower LVEF compared to those without MR.[29] SVR results in a decrease in LV end-diastolic and systolic volumes and percentage of akinetic/dyskinetic myocardium, and an increase in LVEF both at early and late time points following this procedure.[30,31] Torsional mechanics of the LV, specifically of the apex, are impaired among patients with ICM, processes that can be improved following SVR, especially for those patients who have significant preoperative dysfunction.[32] Recently, Doenst et al. reported a fluid-dynamic model that utilizes pre- and postoperative cardiac magnetic resonance imaging to evaluate ventricular flow in patients who have undergone SVR (Fig. 52-9).[33]

DiDonato et al. analyzed the LV shape in patients with ICM using a Fourier (radius of curvature) analysis to determine if the preoperative shape and wall motion abnormalities of the LV following anterior infarction influences outcomes after SVR.[34] Utilizing preoperative echocardiographic images in the 30° right anterior oblique (RAO) axis to examine wall motion and LV shape, three types of LV abnormalities in postinfarction ventricles were characterized (Fig. 52-10). Type 1 represents a true aneurysm with two hinge points, or borders between functional and akinetic/dyskinetic myocardium. Type 2 has one such hinge point, and type 3 is representative of ischemic dilated cardiomyopathy without any hinge points. The amount of functional myocardium is correlated to this classification with type 1 having the most and type 3 the least working myocardium. Not surprisingly, survival was highest among those patients with type 1 morphology, intermediate among those with type 2, and lowest among those with type 3 morphology preoperatively.

One of the most interesting studies of the effect of SVR on cardiac function was performed by DiDonato and colleagues at the Center Cardiothoracique de Monaco.[21] They looked at 30 patients undergoing SVR who did not have electrical dyssynchrony by QRS definition but did have mechanical dyssynchrony. Pressure/volume (P/V) loops were obtained with intraventricular micromanometer-tipped catheters a nd

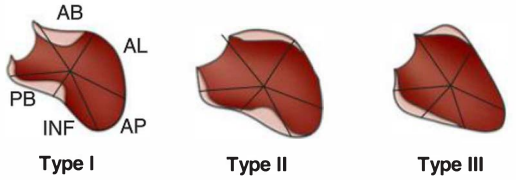



**FIGURE 52-10** Echocardiographic classification of the left ventricle in patients with ICM, (Adapted from DiDonato M, Castelvecchio S, Kukulski T, et al. Surgical ventricular restoration-left ventricular shape influence on cardiac function, clinical status, and survival. *Ann Thorac Surg* 2009;87:455–462. With permission. Copyright Elsevier.)

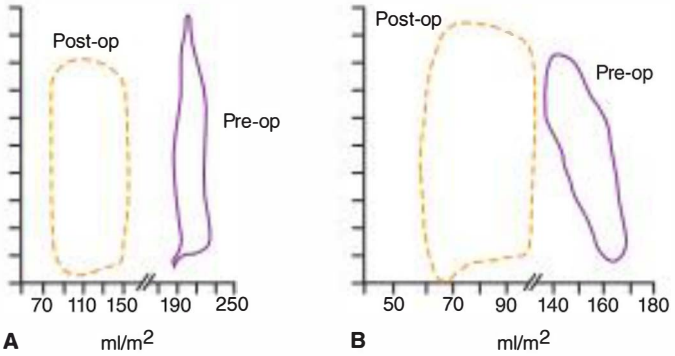



**FIGURE 52-11** Pre- and postoperative pressure volume loops. (Adapted from DiDonato M, Toso A, Dor V, et al. Surgical ventricular restoration improves mechanical ventricular dyssynchrony in ischemic cardiomyopathy. *Circulation* 2004;109:2536–2543. With permission. Copyright Elsevier.)

pressure/length (P/L) loops were created by analyzing ventriculograms utilizing the centerline method at 45 discrete intervals. The P/V loops of these patients were very abnormal in size, shape, and orientation, with impaired isometric phases and a rightward shift. Endocardial time motion was either early or late, yielding P/L loops that were abnormal in size, shape, and orientation. Postoperatively, SVR resulted in a leftward shift of the P/V loops, with their near normalization, as well as normalization of endocardial motion and P/L loops (Fig. 52-11). These physiologic results of SVR occurred in concert with improved EF (30 ± 13 to 45 ± 12 percent), reduced end-diastolic and systolic volume indices (202 ± 76 to 122 ± 48 mL/m$^2$ and 144 ± 69 to 69 ± 40 mL/m$^2$, respectively), a more rapid peak filling rate (1.75 ± 0.7 to 2.32 ± 0.7 EDV/s), peak ejection rate (1.7 ± 0.07 to 2.6 ± 0.09 Sv/s), and calculated measurements of mechanical efficiency.[21]

Schreuder and colleagues further examined the biomechanical impact of SVR on left ventricular function among nine patients who underwent this procedure.[35] Utilizing intraoperatively placed, high-fidelity conductance volume catheters, they studied pressure–volume relationships, energy efficiency, and mechanical dyssynchrony before and immediately after SVR was performed. Mean overall end-diastolic volume was reduced by 37 percent with a concomitant improvement in diastolic function with a 34 percent decrease in $-dP/dt_{max}$. Left ventricular systolic function was significantly improved as evident by a 42 percent increase in $+dP/dt_{max}$, 28 percent increase in peak ejection rate, and 16 percent increase in EF. Left ventricular dyssynchrony was decreased in both systole (33 percent) and diastole (20 percent), leading to an overall 36 percent increase in left ventricular efficiency.

There have been two reports that have specifically examined the effects of SVR on left ventricular diastolic function.[36,37] Some have raised concern that although SVR improves systolic function by eliminating noncontributory myocardium, this reduction in myocardium may lead to a restrictive physiology. The first report examined LV diastolic function in 146 patients who underwent SVR using echocardiographic measurement of transmitral flow patterns.[36] Prior to SVR, LV filling patterns were abnormal in 68 percent, pseudonormal in 19 percent, restrictive in 8 percent, and normal in only 5 percent. After SVR, they found that diastolic function was either unchanged or improved among most patients with 10 percent demonstrating improvement, 72 percent with no change, and worsened in only 18 percent of patients. Those patients with worsened diastolic dysfunction had global ventricular dilation, and those with improvement had dilation of the LV apex only. This group has recently published a longer-term study of diastolic dysfunction among these patients at a median follow-up of 7 months.[37] Again the majority of patients, 78 percent, did not demonstrate any restrictive patterns whereas 22 percent did. Multivariate analysis concluded that preexisting diastolic dysfunction prior to SVR and global dilation of the LV with increased septolateral dimensions were independent predictors of late diastolic dysfunction.

The incidence of ventricular arrhythmias following SVR has been reported by multiple groups with strikingly different results. Early series reported anywhere from a 0 to 3 percent incidence of sudden cardiac death during 5-year follow-up after SVR.[38,39] Other studies reported significant arrhythmias requiring ICD placement in nearly one third of patients who undergo SVR.[40] Two studies reported the incidence of inducible ventricular arrhythmias following SVR, with differing results.[41,42] DiDonato reported on the incidence of ventricular arrhythmias among 382 patients who underwent SVR. In this study, patients underwent preoperative as well as postoperative ventricular stimulation. Preoperatively arrhythmogenic potential was related to the size of the LV; those with LV end-systolic volume index (LVESVI) >120 mL/m$^2$, >100 mL/m$^2$, and <100 mL/m$^2$ exhibited spontaneous, inducible, and no arrhythmias, respectively. Following SVR, sudden cardiac death occurred in only 2.5 percent of patients, and among the entire group, there was an overall decrease in inducible ventricular arrhythmias from 41 percent preoperatively to 8 percent after SVR. O'Neill reported an experience with 217 patients who underwent ventricular stimulation postoperatively following SVR. His group identified significantly

**TABLE 52-3: Retrospective Data for Surgical Ventricular Remodeling**

| Author (Year) | No. of Patients | Operative Mortality (%) | Changes in EF (Absolute Points) | Reduction in End Systolic Volume (%) | 5-Year Survival (%) |
|---|---|---|---|---|---|
| Restore (2004) | 1198 | 5.3[a] | +10 | −29 | 68 |
| Dor (2002) | 1000 | 7.3[c] | +12 | – | – |
| Menicanti (2002) | 985 | 7.2[b] | +10 | −43 | – |
| Mickleborough (2004) | 285 | 2.8 | +10 | −33 | 82 |
| DiDonato/Dor (2001) | 245 | 8.1[d] | +13 | −48 | 82 |
| Kouchoukos (1978) | 145 | 11 | – | – | 73 |
| Di Mattia (1999) | 121 | 6.3 | +18 | – | 73 |
| Lunblad (2004) | 85 | 3.5 | – | – | 91 |
| Cirillo (2004) | 69 | 4.3 | +15 | −47 | – |
| Calafiore (2003) | 50 | 8 | – | – | – |

[a]4 percent without mitral repair.

[b]4.8 percent without mitral repair.

[c]4.8 percent in the last 3 years.

[d]Including mitral repair/replacement.

Data from Menicanti L, DiDonato M. Left ventricular aneurysm/reshaping techniques. *Multimedia Manual of Cardiothoracic Surgery*. 2005.

more patients with postoperatively inducible ventricular arrhythmias (42 percent), but only one death attributable to sudden cardiac death. Criticisms of this study include a more rigorous arrhythmia induction protocol and lack of preoperative induction for comparison. Potential mechanisms for reductions in ventricular arrhythmias include revascularization, mechanical resynchronization, and reduction in volume with ensuing reduction in wall stress, but the impact of SVR on this aspect of post-SVR physiology is not entirely clear.

The group at the Cleveland Clinic investigated the impact of ventricular remodeling on the neuroendocrine axis following SVR. Several markers of the neurohormonal axis are elevated in CHF. This group investigated the plasma levels of norepinephrine, renin, and angiotensin II before and 1 year following SVR as well as brain natriuretic peptide before and 3 months following SVR. They found that SVR reduced norepinephrine by 56 percent, angiotensin II by 60 percent, renin activity by 56 percent, and brain natriuretic peptide by 36 percent.[43]

## OUTCOMES

There is no consensus as to the optimal treatment of ICM. Part of the reason for this is that there are no contemporary prospective randomized trials comparing similar groups of patients between medical therapy and surgical therapies for ischemic heart disease. There are an unlimited number of characteristics that any one study may not specify to ensure that the populations studied are the same as those of other studies. The presence or absence of viability, the presence of targets for revascularization, the location of infarction, and the presence of valvular disease or pulmonary hypertension are but a few making the point.

The published literature on SVR is largely retrospective and nonrandomized.[21] Much of it comes from single-center studies from institutions with a great deal of experience and some published from a limited number of multicenter studies. Although many studies can be criticized for the format, most provide some useful clinical information. A summary of the retrospective data for SVR is presented in Table 52-3.

The effectiveness of SVR can be assessed from a variety of different perspectives. Survival, morbidity, and functional outcomes are the most commonly utilized benchmarks. The optimal technique for performing SVR has not been determined. The personal beliefs of authors have been either implicitly suggested by the surgical technique utilized or studied by direct comparison, usually with a single institutional retrospective study. In a procedure whose functional outcomes are in part based on changing the size and shape of the heart, morphologic assessments are important considerations. A recent analysis of over 12,000 patients who underwent SVR from 1980 to 2005 utilizing a variety of surgical techniques was recently published by Klein et al.[44] This analysis found that endoventricular repair was associated with a reduced risk of both early- and late-term mortality compared to linear repair. Regardless of the technique employed, the addition of CABG was associated with improved outcomes and mitral valve repair with poorer outcomes in this large patient cohort. This is not surprising since most studies report that the need for mitral repair indicates a sicker patient population with advanced remodeling and larger ventricles.

### Retrospective Studies

The RESTORE group is a collection of international centers performing SVR that have combined data to study the outcomes of the SVR procedure.[45] The combined number

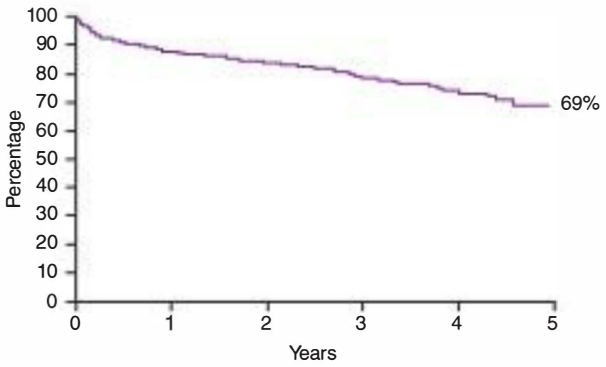



**FIGURE 52-12** Overall 5-year survival curve from the RESTORE group. (Adapted from Athanasuleas CL, Buckberg GD, Stanley AW, et al. Surgical ventricular restoration in the treatment of congestive heart failure due to post-infarction ventricular dilation. *J Am Coll Cardiol* 2004;44:1439–1445. With permission. Copyright Elsevier.)

of patients followed up by this group is 1198, operated on between 1998 and 2003. Most patients were in NYHA class 3 (40 percent) and class 4 (29 percent). Concomitant procedures included CABG in 95 percent, mitral valve repair in 22 percent, and replacement in 1 percent. This study represents what is probably the best large study to date in performing SVR in a heart failure population. The RESTORE investigators found that global systolic function increased postoperatively and ventricular size decreased as measured by ventriculography, magnetic resonance imaging, or echocardiography. The EF increased from 29.6 ± 11 to 39.5 ± 12.3 percent. The LVESVI decreased from 80.4 ± 51.4 mL/m$^2$ to 56.6 ± 34.3 mL/m$^2$. Survival was excellent in this group. Thirty-day mortality was 5.3 percent, and the overall 5-year survival was 68.6 ± 2.8 percent (Fig. 52-12). Logistic regression analysis was performed to identify risk factors for death at any time following surgery. These included preoperative EF below 30 percent, LVESVI above 80 mL/m$^2$, advanced NYHA functional class, and age above 75 years. Patients with an EF below 30 percent had a survival of 63.8 ± 3.9 percent compared to 76.7 ± 3.2 percent for those with an EF above 30 percent and 83.0 ± 4.0 percent with an EF of greater than 40 percent. The fact that many of these risk factors are the same or similar to those identified by both Menicanti and Mickleborough suggests the ability of single institutions to discover the same findings as seen in multicenter studies.

Menicanti and colleagues from Milan reported their large experience of over 1000 patients who underwent SVR. The overall operative mortality was 7.2 percent and was lower (4.8 percent) in patients who underwent concomitant CABG, and higher in patients with a preoperative EF below 30 percent (12.3 percent), with concomitant mitral valve procedures (15 percent), and in patients with NYHA class 4 symptoms (15.2 percent).[46] What is not easy to discern in this or any other single-institutional experience is exactly what the interplay of two or three of these factors is, but it is logical that the risk would be higher. These investigators have identified that factors associated with adverse outcomes include worse NYHA functional class, EF below 20 percent, age above 70 years, urgent intervention, mitral valve procedure, pulmonary hypertension (pulmonary artery systolic pressure >60 mm Hg), larger ventricles (end-diastolic volume index >180 mL/m$^2$), the number and sites of previous MIs, and right ventricular dysfunction.[19]

Mickleborough and colleagues reported on 285 patients over a 20-year period utilizing a linear closure technique with (25 percent) or without septoplasty (75 percent).[24] The excellent 5- and 10-year survival rates were 82 and 62 percent, respectively. As mentioned above, it is unclear whether the patient populations are the same. The study group included posterior infarcts and the data are presented together. In the anterior infarct group (appropriate for SVR), only 62 percent had CHF of unknown severity despite having a low EF (mean 24 + 11 percent). Patients had to have a palpably thinned area in the anterior wall, and severe mitral regurgitation was an exclusion criterion (only 1 percent had a valve intervention. Moreover, the presence of calcified aneurysms excluded some patients. Despite these differences, the risk factors for poor outcomes were EF below 20 percent, CHF, ventricular tachycardias, and hypertension—in all, not too dissimilar from the conclusions of other investigators.[22,47–49]

The group at the Cleveland Clinic have reported their decade of experience performing SVR in 220 patients.[50] NYHA class 3 or 4 symptoms were present in two-thirds of patients, and mean preoperative LVEF was 21.5 percent. Nearly half of patients underwent either mitral valve repair or replacement along with SVR. LVEF improved from 21.5 to 24.7 percent, and significant MR (>1+) was reduced from 49 to 26 percent after SVR. Perioperative 30-day mortality was 1 percent, and 1-, 3-, and 5-year overall survival rates were 92, 90, and 80 percent, respectively. Factors associated with increased mortality included EF <20 percent, BMI <24, QRS >130 ms, postoperative renal failure, and prolonged ICU stay.

Our group at Johns Hopkins has looked at the outcomes of groups of patients with severe advanced CHF. In one study, 100 percent of the patients had class 3 (34 percent) or class 4 (66 percent) CHF and an EF by magnetic resonance imaging below 20 percent, with 65 percent having an EF below 15 percent. Despite how sick these patients were, 69 percent improved to NYHA class 1 or 2, with a 1-year survival of 81 percent. Cox regression analysis demonstrated that preoperative diabetes, the use of an intra-aortic balloon pump during surgery, incomplete revascularization, and a preoperative LVESVI greater than 130 mL/m$^2$ were significant predictors of overall mortality.[49]

The Hopkins group also looked at the outcomes of SVR in patients who had multiterritory infarctions that had been contraindications in all previously published series. The finding that standard treatment of the anterior wall infarction, along with suture plication of the inferior wall for infarctions in the territory of the right coronary artery and the lateral wall for infarctions in the lateral wall opens the door to a potentially new patient population for this procedure.[22]

## Prospective Randomized Clinical Trials

With regard to the addition of SVR to conventional CABG for revascularization, there have been two recent prospective randomized clinical trials comparing revascularization with revascularization plus SVR in patients with ischemic heart disease.[12,51]

Riberio and colleagues reported on 74 patients with an EF less than 35 percent, LVESVI greater than 80 mL/m$^2$, and akinetic anterior wall motion who were randomized to either revascularization with CABG ($n = 35$) or revascularization plus SVR utilizing the endoventricular technique ($n = 39$) at a single institution.[51] Patients with significant valvular pathology were excluded with the exception of grade 1–2 MR. There were no significant differences among preoperative characteristics of either group; specifically with regard to age, LVEF, number of diseased coronary vessels, percent of LV asynergy, MR, or NYHA class. CABG was performed in a similar manner for both groups, and the only difference between the operative characteristics among groups was that the group with SVR predictably had longer CPB times. There were no differences in perioperative morbidity or mortality. Left ventricular size as measured by LVESVI immediately postoperatively and at 2-year follow-up was significantly less for those patients undergoing SVR compared to those undergoing CABG alone (62 and 65 mL/m$^2$ vs 91 and 98 mL/m$^2$, respectively). At the end of follow-up there were significant differences in outcome between the two groups. Postoperatively at the 2-year follow-up, LVEF was improved for both groups. However, the increase was greater for the group with SVR (30.5–46.5 percent vs 29.0–38.0 percent, $p < 0.001$), and over two-thirds of patients who underwent SVR had an increase of greater than 10 percent LVEF. NYHA class symptoms were improved in both groups, but the degree of improvement was greater in the CABG plus SVR group (2.3 vs 1.4, $p < 0.001$). Recurrent heart failure (26.4 vs 2.6 percent, $p < 0.001$) and severe MR (17.6 vs 0 percent, $p = 0.02$) were worse in the group who underwent CABG alone. Although there was no difference in overall mortality between the two groups, event-free time (all causes of death, MI, recurrent heart failure) following surgical intervention was significantly increased in the group who underwent CABG and SVR ($p = 0.016$). Although conducted in a randomized, controlled fashion and demonstrating a difference in outcomes, the overall number of patients in this study is quite small.

The STICH trial was an NIH-funded multicenter trial investigating the relative benefits of medical therapy, CABG, and CABG + SVR in treating ICM.[52] Hypothesis 2 of the funded study was designed to investigate the benefit of adding SVR to CABG in patients with an LVEF less than 35 percent, with revascularizable CAD, who were candidates for SVR based upon an ESVI of >60 mL/m$^2$, and with documentation of nonviability of the anterior wall. In this arm of the study, the plan was to enroll 1000 patients in 50 centers. The primary outcome was death from any cause or hospitalization for any cardiac cause. Patients with recent MI, planned PCI, significant aortic valvular pathology, and those with additional comorbidities and a life expectancy of less than 3 years were all excluded. All patients underwent CABG with particular methods at the discretion of the surgeon. SVR was performed according to surgeon preference with or without patch repair. However, the surgical therapy committee mandated that surgeons could use "any ventricular reconstruction method that consistently results in a low operative mortality, and average EF increase of ≥10 percent and an average LVESVI decrease of ≥30 percent as assessed by the 4-month postoperative CMR measurement.[52] All patients were optimally medically managed at the discretion of their primary heart failure team.

The initial findings were that there were no significant differences among preoperative characteristics in either group with respect to age, medical comorbidities, Canadian Cardiovascular Society (CCS) angina symptoms, NYHA class, LVEF, LVESVI, percent LV akinesia, MR, number of diseased coronary vessels, or heart failure medications. Thirty-day perioperative mortality was identical (5 percent) among those undergoing CABG and those with CABG plus SVR. Both groups experienced a statistically significant improvement in the CCS angina class and the 6-min walk test as well as NYHA class, but there were no statistically significant outcome differences between the CABG alone and CABG plus SVR groups. The primary outcome of death from any cause or hospitalization for cardiac reasons was similar for both the CABG and CABG plus SVR groups (59 vs 58 percent). The CABG group and CABG plus SVR groups were not different with respect to death from any cause (28 vs 28 percent), hospitalization for any cause (55 vs 53 percent) or cardiac causes (42 vs 41 percent), or subsequent MI (4 vs 4 percent). Subset analyses failed to identify any differences between the two groups and the accompanying editorial concluded that the addition of SVR to CABG for patients with ICM is not justified based upon these results.[53]

There were, however, many criticisms of the design of the study and the manner in which it was conducted.[54,55] Patient selection was a specific criticism of the study. The requirement for documentation of nonviability was dropped and the enrolled patients had to only demonstrate "dominant anterior LV dysfunction."[12] It is well known that viable muscle can demonstrate abnormal wall motion by echocardiography and the demonstration of akinesis or dyskinesis by echocardiography does not meet the threshold standard for proving nonviability.[55–57] SVR has never been recommended for patients with viable myocardium. The second major criticism concerns the adequacy of the SVR procedure. The average LVESVI reduction in this trial was only 19 percent. This degree of LVESV reduction is far less than the average of 40 percent as has been previously reported in large, nonrandomized trials of SVR, suggesting that the operations may not have been properly performed according to current practice.[55] In addition,

as reported by Michler et al. at the 2010 meeting of the American College of Cardiology in Atlanta, the majority of patients (>60 percent) had either no reduction or less than 30 percent reduction in LVESVI.[58] Patients were divided into three groups based upon echocardiographic measurement of postop LVESVI: group 1 was ≤ 60 mL/m², group 2 60–90 mL/m², and group 3 >90 mL/m². He found that in group 1 only 28 percent had an LVESVI reduction of ≥30 mL/m² with 43 percent having no reduction; 38 percent in group 2 had a reduction >30 mL/m² with 20 percent having no reduction, and 44 percent in group 3 had a reduction with 21 percent having no reduction. In addition, no patient had a 10 percent improvement in EF. This supports concerns over the quality of the surgical recommendations.

A recent study by DiDonato et al. demonstrated that postoperative LVESV is an independent predictor of survival following SVR and suggested that this may explain the lack of difference with the addition of SVR in the STICH trial.[59] To qualify as a surgeon for this study, surgeons had to demonstrate a mortality of <5 percent in 25 patients having undergone CABG in patients with an EF of <40 percent, an operative mortality of <10 percent, and an LVESVI reduction of 30 percent in 5 SVR cases.[52] There is no report that this threshold was met. Trial expansion to 127 sites due to poor enrollment led to an average of four operations per site. Critics suggest that to properly evaluate the outcome in this cohort of patients, only those patients who have documentation of nonviability and documentation of an adequate SVR procedure as defined by the STICH surgical therapy committee should be included. Until then, the STICH trial fails to answer the question in the Hypothesis 2 it was intended to answer.

## CONCLUSIONS

In summary, SVR is a procedure that has evolved from a treatment for ventricular aneurysms to become a treatment for CHF. It has been shown to improve ventricular size, morphology, LVEF, stroke-volume index, endocrine markers of CHF, ventricular energetics, ventricular synchrony, and mechanical efficiency. Clinically, it results in improved functional capacity (NYHA class) and an excellent 5-year survival in very sick patients. It is an excellent treatment option in appropriately selected patients with ICM. The results from two separate randomized clinical trials are not congruous, and future larger, well-designed studies may be necessary to determine the eventual role of SVR in the treatment of ICM. Where SVR will fit in the armamentarium of a heart failure team will be institution-dependent based on their expertise and experience. Further studies are needed to better define the appropriate patients, the basis of the beneficial response (ventricular physiology versus relief of ischemia), the optimal technique, and the appropriate time to perform the procedure. Much remains to be worked out.

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## SURGICAL VENTRICULAR REMODELING BOARD REVIEW QUESTIONS (CHAPTER 52)

1. Which is true regarding the pathophysiology of ICM-induced ventricular remodeling?
   A. There is an increase in the end-systolic diameter and volume of the LV.
   B. Development of concomitant mitral insufficiency worsens global systolic function.
   C. Progressive dilation of the LV eventually leads to aortic insufficiency.
   D. The ventricle becomes more elliptical shaped.
   E. Wall stress is decreased as the ventricle thins and dilates.

2. Which is not an indication for SVR?
   A. Asynergy of greater than 35 percent of the LV
   B. Enlarged LV with end-diastolic volume index >120 mL/m$^2$
   C. Akinetic anterior wall
   D. Reduced right ventricular function
   E. Clinical evidence of CHF

3. Which of the following is a relative contraindication to surgical ventricular restoration?
   A. Single area of infarction
   B. Pulmonary hypertension
   C. Presence of concomitant coronary artery disease
   D. Presence of severe mitral insufficiency
   E. Presence of severe tricuspid insufficiency

4. Which is not a goal of surgical ventricular restoration?
   A. Revascularization of all viable territories
   B. A reduction in the size of nonfunctional anteroseptal myocardium
   C. Repair of concomitant valvular regurgitation
   D. Recreation of the elliptical shape of the LV
   E. Retention of nonfunctional myocardium to prevent arrhythmias

5. Physiologic changes following SVR include which of the following:
   A. Decrease in both LV end-systolic and end-diastolic volumes
   B. No change in LV ejection fraction
   C. Increase in plasma norepinephrine
   D. Reduced LV torsional mechanics
   E. Reduced peak filling rates

## ANSWERS

1. **Answer: B.** The development of concomitant mitral insufficiency worsens systolic function. There is an increase in the end-diastolic diameter and volume, and the ventricle becomes more spherical shaped. This dilation does not lead to aortic insufficiency and increases wall stress.
2. **Answer: D.** Biventricular failure is a contraindication to surgical ventricular restoration. Asynergy of greater than 35 percent of the LV, LVEDVI >120 mL/m$^2$, an akinetic anterior wall, and clinical evidence of CHF are all acceptable indications to consider surgical ventricular restoration.
3. **Answer: B.** Pulmonary hypertension is a relative contraindication. A single area of infarction is ideally treated with surgical ventricular restoration. Other concomitant cardiac disease, such as coronary artery disease or valvular insufficiency, can be successfully addressed at the same operation.
4. **Answer: E.** All nonfunctional myocardium should be removed to reduce the size of the ventricle. Retention of diseased, nonfunctional myocardium may be a focus of arrhythmogenesis. Concomitant coronary artery disease and valvular regurgitation should be addressed, and the LV restored to a more normal, elliptical shape.
5. **Answer: A.** Both LV end-systolic and end-diastolic volumes are decreased. LV ejection fraction, torsional mechanics, and peak filling rates are all increased. Plasma norepinephrine levels are decreased.

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# Stem Cells for Cardiac Surgical Disease

*Peter V. Johnston*
*Gary Gerstenblith*

**KEY CONCEPTS**

- There are an estimated 5.8 million people in the United States with heart failure.[1]
- Stem cell therapy for the heart represents a novel method by which dysfunctional cardiac tissue might be repaired or replaced, thereby alleviating heart failure and decreasing or eliminating life-threatening arrhythmias.
- Potential sources of stem cell therapy for the heart include the bone marrow, circulating progenitor cells, embryonic stem cells, and the heart itself.
- Multiple modalities exist for delivery of stem cell therapy to the heart, including traditional and minimally invasive surgical methods as well as intravenous and percutaneous catheter-based techniques.

## INTRODUCTION/BACKGROUND

The heart was once thought to be a terminally differentiated organ, with no cell turnover or repair; the cardiac myocytes at the time of early adulthood were all the cells a person would ever have. It was for this reason that myocardial infarction (MI) was thought to be such a devastating event, as there was no native ability to repair or replace damaged heart tissue. This understanding began to change in the 1990s, when investigators first reported the presence of cardiac myocytes in various stages of cell division, found during histologic analysis of myocardial tissue.[2] Since that time it was learned that the heart does have the capacity for cellular repair, both from stem cells resident in the heart, and from so-called "circulating" progenitor cells, which, following release from the bone marrow, may traffic to and enter heart tissue to effect repair.[3–5] This endogenous repair system appears to have the capacity to handle routine cellular turnover, that is, normal "wear and tear" on the heart, but becomes overwhelmed in the setting of a sudden large insult, such as a MI, with the default fibroblast scar formation. With the discovery of the capacity for cellular repair of the heart, interest in augmenting or optimizing this system to the point that the damaged and failing heart could be biologically repaired has grown. For example, although the small number of resident cardiac stem cells (CSCs) might be insufficient to repair the damage of a large infarction, removal and expansion of these cells in ex vivo tissue culture might generate sufficient numbers of cells to result in a therapeutic benefit.

The interest in cell therapy is driven primarily by the nearly 6 million Americans with heart failure,[1] as well as millions of others throughout the world, many of whom, despite optimal medical therapy, suffer significant morbidity and mortality from their condition. In many cases, temporary mechanical support or heart transplantation is necessary, but supply constraints and large expense limit availability. Thus, the great hope for cellular therapy for the heart is that end-stage heart failure could be eliminated by preventing or reversing the deleterious remodeling that occur following significant injury to the heart. Although such benefits are reported in animal models, clinical cell therapy for the heart remains in its infancy, and numerous questions remain regarding which cell type (or types) might be most effective at cardiac repair, when and how those cells should be delivered, and finally, the mechanisms by which the cells achieve any benefit. Below, the current state of cell therapy for the heart, focusing on results and lessons learned from those clinical studies reported to date, will be discussed, couched in the understanding that this field at present is young and rapidly changing.

## STEM CELLS USED FOR THERAPY OF THE HEART

To date, numerous different types of stem cells have been studied in clinical trials of cellular therapy for the heart. Here we discuss these different cell types, their potential advantages and disadvantages, and the clinical results to date (see also Table 53-1).

### Bone Marrow–Derived Stem Cells

#### BONE MARROW MONONUCLEAR CELLS

Perhaps the best characterized and most widely studied form of cell therapy for the heart is that using stem cells isolated from the bone marrow. In addition to serving as hematologic precursors, certain populations of bone marrow cells (BMCs) are released into the blood in response to signals from injured tissue, and subsequently traffic to and enter injured tissues or organs to assist in repair.[6] BMCs were first shown to be capable of cardiac repair in 2001, in experiments in which cells were injected at the infarct border zone of small animals.[7] A portion of these cells engrafted and subsequently differentiated into cardiac tissue, forming myocytes, smooth muscle, and vascular cells. Little more than a year later, in late 2002, the first clinical trial of stem cell therapy for the heart was reported, when the results of the TOPCARE-AMI trial were published.[8] In this study, patients who had suffered a recent MI were randomized to receive intracoronary infusion of BMCs, circulating progenitor cells (CPCs), or to serve as a control. The results were promising, in that those patients who received either cell type had significantly improved left ventricular ejection fraction (LVEF) 4 months later compared with controls (results discussed in detail below).

Since the publication of TOPCARE-AMI, more than 800 patients have been enrolled in randomized control studies of BMC therapy for the heart, and generally these trials show a modest benefit.[9–27] In a meta-analysis of the trials published as of 2007, BMC therapy after MI resulted in modest, but statistically significant improvements in measures of left ventricular (LV) function and remodeling compared with placebo (see Fig. 53-1).[9] For example, patients receiving cell therapy had a 3.64 percent greater improvement in LVEF, compared with placebo (95 percent CI: 1.56 to 5.73). Similar modest, but significant relative benefits were seen in terms of infarct size and change in LV end systolic volume (ESV) across studies, as well as modest, but nonsignificant differences in end-diastolic volume. Perhaps most importantly, across studies BMC therapy was safe, suggesting that the modest beneficial effects did not come at a safety cost. These results have led to the question of how the beneficial effects of BMC therapy might be further augmented and optimized. Closer examination of specific BMC clinical studies led to certain conclusions that will guide future studies.

Of the studies of BMC therapy for the heart to date, the results of the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial, published in 2006, are perhaps the most informative.[10] In this study, patients suffering an ST-elevation MI were randomized to receive autologous BMCs or placebo (carrier solution only) by intracoronary infusion in the infarct-related artery. A total of 204 patients were enrolled (101 receiving cells, 103 receiving placebo), and were followed for 1 year. As with the overall findings for BMCs, the effect of cell infusion on cardiac function in this

**TABLE 53-1: Comparison of Stem Cell Types Studied for Cardiac Therapy**

| Stem Cell Type | Advantages | Potential Disadvantages |
|---|---|---|
| Bone marrow cells (BMCs) | Readily available<br>Extensive clinical experience<br>Clinically safe | Ability to form new cardiac tissue unclear<br>Clinical effects modest to date |
| Mesenchymal stem cells (MSCs) | Immune privileged allowing for delivery to allogenic recipient<br>Evidence of benefit from systemic delivery<br>May reduce arrhythmias following infarction | Large cell diameter may limit certain delivery methods (e.g., intracoronary infusion) |
| Circulating progenitor cells (CPCs) | Participate in vascular repair and neoangiogenesis<br>Circulating levels correlate with clinical outcomes | Mixed results in clinical trials to date<br>May not be effective in chronic heart failure |
| Cardiac stem cells (CSCs) | Cardiac-specific<br>Capable of forming new myocardium<br>May be of benefit in nonischemic cardiomyopathy | Isolation and expansion can take weeks to months<br>Cell diameter may limit certain delivery methods (e.g., intracoronary infusion) |
| Skeletal myoblasts | Abundant source of stem cells<br>Resistant to hypoxia | Associated with malignant arrhythmias in MAGIC Trial |
| Embryonic stem cells | Unlimited differentiation potential | Intracardiac teratoma formation in animal models<br>Ethical concerns |

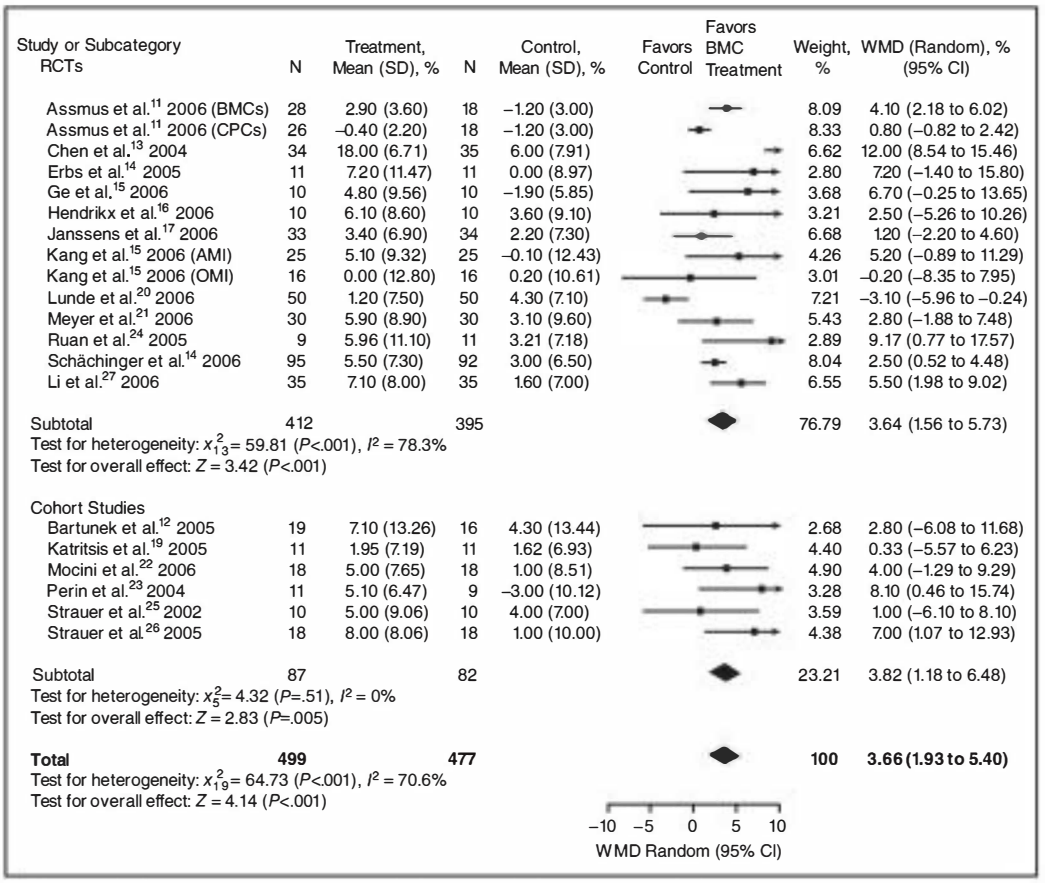



**FIGURE 53-1** Forest plot of unadjusted difference in mean change in left ventricular ejection fraction [with 95 percent confidence intervals (CIs)] in patients treated with bone marrow–derived cells (BMCs) compared with controls from multiple randomized control trials (RCTs) and cohort studies. The overall effect was statistically significant in favor of BMC therapy. (Adapted with permission from Abdel-Latif A, Bolli R, Tleyjeh IM, et al. Adult BMCs for cardiac repair: A systematic review and meta-analysis. *Arch Intern Med* 2007 May 28;167:989–997. Copyright © (2007) American Medical Association. All rights reserved.)

study was modest, but significant, with the LVEF at 3 months in those who received cell therapy significantly greater than in those who received placebo (53.8 vs. 49.9 percent, $p = 0.02$). Cell-treated patients also had a significantly greater absolute increase in LVEF over 3 months (5.5 vs. 3.0 percent, $p = 0.01$). Although the effects on systolic function were also modest, they were associated with significant clinical benefits at 1 year. There were two deaths, no infarctions, and 21 revascularizations in the BMC group and six deaths, five infarctions, and 35 revascularizations in the placebo group, for a significantly lower rate of the combined outcomes in the BMC group ($p = 0.01$).

This study was particularly informative, however, when the results were further scrutinized. First, the patients who suffered the largest infarcts (as evidenced by the most severe LV dysfunction) benefited the most from cell therapy. When patients were stratified by their LVEF prior to treatment to above or below the median (48.9 percent), those patients with an EF below the median who received BMCs had a mean absolute increase in LVEF of 7.5 percent compared with only 2.5 percent in those receiving placebo ($p = 0.002$). However, in those patients whose baseline LVEF was above the median, cell therapy resulted in a mean absolute increase of only 4.0 percent, nearly identical to the 3.7 percent increase in such patients treated with placebo ($p = 0.81$; see Fig. 53-2A). These results indicate that the overall benefit seen in the study was driven primarily by those with a baseline LVEF below the median, and this finding is not surprising, as those patients with an LVEF greater than the median had essentially normal systolic function (~55 percent in adults), suggesting that the damage suffered from their infarction was limited. This suggests that those patients with significant damage and dysfunction are the ones who stand to benefit the most from cellular therapy and should be targeted for future clinical study.

The REPAIR-AMI study was also informative in that the timing of cell delivery proved important, and the findings were contrary to what might be expected. While many believed that earlier delivery would be better, in fact the

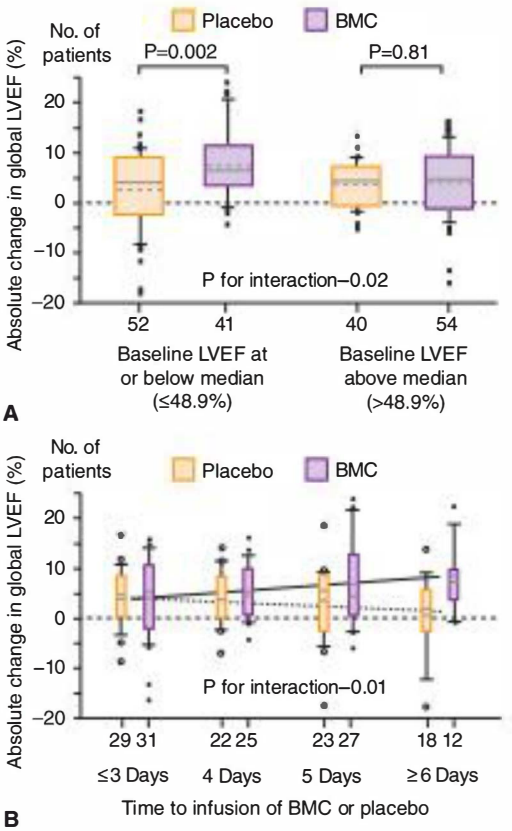



**FIGURE 53-2** Effect of baseline left ventricular ejection fraction (LVEF) and timing of intracoronary infusion of BMCs on absolute change in LVEF from the REPAIR-AMI Trial. Panel **A** shows that in those patients whose baseline LVEF was below the median (<48.9 percent), BMC treatment resulted in a significant increase in LVEF compared with placebo (left side of panel **A**). In contrast, no significant difference was seen between the treatment groups in those patients with a baseline LVEF above the median (right side of panel A). Panel **B** shows the effect timing of intracoronary infusion had on the relative effect of BMC therapy compared with placebo. When given <3 days after MI, there was no difference in absolute change in LVEF between BMC, and placebo-treated patients; however, the further from the time of MI, the greater the relative benefit of BMC therapy ($p = 0.01$ for interaction). (Reproduced with permission from Schachinger V, Erbs S, Elsasser A, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med* 2006 Sep 21;355(12):1210–1221. Copyright© (2006) Massachusetts Medical Society. All rights reserved.)

opposite proved true. In the study, patients received treatment between 3 and 7 days after their infarction. This variability resulted from differences in the time required for cell processing and other scheduling logistics, and was not a prespecified point of investigation. However, when patients were stratified by the day after infarction that they received their infusion, there was a direct relationship between time and absolute increase in LVEF, with those receiving BMCs later having greater improvement in systolic function, and the greatest difference compared to time-matched controls (see Fig. 53-2B). This would suggest that delivering cells to an area of new infarction, which is inflamed and filled with large numbers of dead or soon-to-be-dying myocytes, is delivering them to a hostile environment, which likely reduces BMC survival and engraftment, thereby limiting their effectiveness. It remains to be seen what the optimal time is for cell delivery to the heart after acute MI, as there is likely a point after which there are diminishing returns, but REPAIR-AMI has certainly indicated that early delivery is not optimal.

The TOPCARE-CHD Trial of BMC therapy in chronic LV dysfunction was published[11] at the same time as REPAIR-AMI. There are many patients who develop ischemic cardiomyopathy well after their infarction, or have unrecognized or "silent" MIs, and only present sometime later with heart failure. In many ways such patients are those who stand to benefit most from cell therapy, as when their cardiomyopathy is discovered, they often receive limited benefit from revascularization. In TOPCARE-CHD, 75 patients who suffered a MI at least 3 months prior to enrollment, with a well-demarcated area of LV dysfunction, and a patent infarct-related artery, were randomized to receive intracoronary infusion of BMCs, CPCs, or to serve as a control (no cell infusion). The cells were delivered via intracoronary infusion in the infarct-related artery. After 3 months, there was a cross-over phase in which all patients received a second infusion of cells. Patients receiving cells at the first infusion received the other cell type at the second infusion, and placebo patients were randomized to one of the two cell types. The subjects were then followed for three additional months.

The primary outcome of the TOPCARE-CHD study was absolute change in LVEF. Patients receiving BMCs had a modest but significant increase in LVEF (+2.9 percent, $p = 0.001$ compared with baseline), while CPC treated (−0.4 percent, $p = 0.60$), and control patients (−1.2 percent, $p = 0.12$) did not. The significant increase in LVEF following administration of BMCs was present regardless of whether they were given as the initial treatment, or following administration of CPCs. There was also a trend toward lower adverse clinical outcomes 3 months after initial treatment in patients receiving BMCs. Using the combined end point of death, MI, stroke, rehospitalization for heart failure, or ventricular tachycardia, no patients treated with BMCs experienced these events, compared with five patients in the CPC group (15 percent), and three in the control group (13 percent; $p = 0.07$ across groups). These results suggest that patients with remote prior MI can still benefit from cell therapy, from both LV function and clinical standpoints. This benefit, however, appears limited to BMCs, as CPCs did not produce the same results. Although these results would indicate that not all stem cells have equal benefit, it should be interpreted cautiously as the mean dose of BMCs in this study was 205 million cells, while that for CPCs was only 22 million. The lack of effect seen with CPCs in this study may therefore be a function of cell dose rather than type.

Together the results from the BMC clinical trials to date support the promise of stem cell therapy for the heart,

though admittedly the modest functional benefits have tempered clinical enthusiasm. There is the hope that the beneficial effects of BMCs can be improved upon in the future as parameters of patient selection, delivery timing, and dosing are further understood and optimized. Although the answers to these questions will require further clinical studies, the excellent safety profile of BMC cell therapy to date suggests that from an ethical standpoint, these can be pursued.

## MESENCHYMAL STEM CELLS

Mesenchymal stem cells (MSCs) are a subpopulation of the bone marrow, which are involved with repair of tissues of mesenchymal origin, including muscle, bone, and adipose tissue.[28,29] They are multipotent and directable in their ultimate fate, so they have been used experimentally to treat not only bone and connective tissue disorders, but heart disease as well. In addition, they have potent immunomodulatory effects resulting from their ability to alter T-cell activation, thereby limiting inflammation and cell killing. Most importantly for cell therapy of the heart, the immunomodulatory effects of MSCs mean that they are relatively immune-privileged, and do not stimulate a typical rejection response when delivered to an allogeneic recipient.[30] This has led to the concept that MSCs may be an ideal cell for early treatment of tissue injury, as allogeneic MSCs could potentially be stored like a drug, ready to be delivered at any time, "off-the-shelf."

The ability of MSCs to take on a cardiac phenotype when delivered to the heart was first reported by Toma and colleagues in 2002, and led to further trials of MSCs for "cellular cardiomyoplasty."[31] In this study, human MSCs, delivered by direct injection to the normal (noninfarcted) hearts of adult immunodeficient mice, engrafted, and over time came to resemble cardiac myocytes, both morphologically and by surface marker expression. This finding was followed quickly by multiple studies in large animal models. Perhaps most relevant to the content at hand are the results reported by Shake et al. later the same year. They reported that when autologous MSCs were delivered by direct surgical injection to the hearts of pigs 2 weeks after creation of an infarction, the cells engrafted and significantly attenuated the wall thinning and regional dysfunction typically seen after an infarction, as compared with control animals.[32] These findings were supported by multiple subsequent studies of MSC treatment in large animal models of MI and ischemic cardiomyopathy using various cell delivery modalities, including catheter-based endocardial injection.[33–36]

The first clinical trials of MSCs in the heart, like those involving BMCs, were performed using intracoronary infusion after MI. These studies by Chen et al.[13] and Katritsis et al.[19] were small (and in the latter only case-controlled), but showed promising effects in terms of attenuation of LV remodeling and preservation of cardiac function. Neither study reported complications related to intracoronary MSC infusion, which contrasted with multiple animal studies, which reported that such delivery can be complicated by MI due to vascular congestion.[37–39] This may reflect a difference between the coronary vascular capacitance of human and large animal models, though safety concerns have limited further trials using intracoronary infusion to deliver MSCs.

Perhaps one of the more important studies of MSC therapy to date is the Safety Study of Adult Mesenchymal Stem Cells to Treat Myocardial Infarction study, the results of which were published in 2008.[40] In this double-blind placebo-controlled study, patients within 10 days of a first ST-elevation MI were randomized to receive systemic intravenous infusion of allogeneic MSCs or placebo. Overall there was no significant improvement or difference in LVEF in those patients treated with MSCs compared with placebo, but in the subset of patients who had suffered an anterior MI, MSC infusion resulted in significant improvement in LV ejection fraction at 6 months (+7.3 ± 3.4 percent, $p = 0.044$, $n = 12$), while placebo treatment did not (3.4 ± 3.4 percent, $p$ = NS, $n = 8$). Anterior MIs are those most likely to result in significant LV dysfunction, and thus the results of this study are similar to those of REPAIR-AMI, in that those patients with more LV dysfunction experienced greater benefit from BMC therapy.[10] In addition, patients receiving MSCs had significantly fewer arrhythmic events over the 6-month follow-up period: only one patient in the MSC group (2.9 percent) had nonsustained ventricular tachycardia as compared with five patients who received placebo (26.3 percent; $p = 0.018$). Arrhythmic events after MI (and in heart failure in general) are a primary cause of morbidity and mortality, and therefore the antiarrhythmic effect of MSC treatment seen in this study is important. Furthermore, one of the potential concerns about cell therapy for the heart is that delivered cells could be a focus for arrhythmia,[41] thereby negating any functional benefit. Indeed, in the Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial of intramyocardial injection of skeletal myoblasts for treatment of LV dysfunction (discussed below), cell therapy proved proarrhythmic.[42]

In summary, based on the results of studies done to date, the use of MSCs to treat cardiac dysfunction and repair the heart after infarction is being actively pursued for treatment of both acute and chronic ischemic disease, as well as for dilated (nonischemic) cardiomyopathy. Numerous studies are currently underway to explore the best delivery method, and whether there is an efficacy difference between autologous and allogenic MSCs. If allogenic MSCs are as effective as autologous cells, their use would eliminate the need to isolate and expand cells from each patient, and potentially make cell therapy for the heart more practical and cost-effective.

## CIRCULATING PROGENITOR CELLS

First described by Asahara et al. in 1997,[43] CPCs, or endothelial progenitor cells (EPCs), as they are sometimes called, are a subpopulation of BMCs that can be found in the blood and express surface markers typical of both hematopoietic and endothelial cells.[44] They are able to differentiate into

mature endothelial cells, and contribute to vascular repair and creation of new blood vessels. They are stimulated by, and their concentration in the blood increases in response to, vascular injury or inflammation. Furthermore, their relative abundance in the blood is a predictor of vascular function and health and has been correlated with cardiac risk factor prediction models such as the Framingham Score.[45]

The ability of CPCs to contribute to neoangiogensis and vascular repair makes them a logical choice for the treatment of MI and ischemic cardiomyopathy, and to date CPCs have been studied in multiple clinical trials with mixed results. The potential beneficial effects of these cells were seen in the TOPCARE-AMI study. Twenty patients suffering an ST-elevation MI were randomized to receive intracoronary infusion of autologous BMCs ($n = 9$), or CPCs ($n = 11$).[8] Treatment with either cell type resulted in an increase in LVEF and a significant reduction in ESV, a marker of adverse remodeling, compared with baseline at 4 months after treatment. In the CPC group patients had an average absolute increase in LVEF of 8.2 percent (51.3–59.5 percent), and decrease in ESV of 8.0 mL (56.9–48.9 mL). These results were nearly identical to those seen in the BMC group, and when all patients receiving cell therapy were pooled, the changes in LVEF and ESV from baseline to 4 months were significant ($p = 0.003$ and 0.011, respectively). There was no placebo group in this study, but LVEF and ESV in case-matched control patients ($n = 11$) who were enrolled and followed in the study did not significantly change. At 4 months, patients receiving cell therapy (CPC and BMC pooled) had a significantly greater mean LVEF compared with control patients (60.1 vs 53.5 percent, $p < 0.05$), and a significantly different change in ESV (−13.8 mL vs + 7.8 mL, $p < 0.02$).

The same benefits of CPC infusion were not present, however, in the TOPCARE-CHD Trial, comprised patients with chronic LV dysfunction due to MI. As discussed above, in this study patients who had suffered an MI at least 3 months prior to enrollment were randomized to receive intracoronary infusion of BMCs, CPCs, or placebo[11] in the infarct-related artery, and only those patients receiving BMCs had benefit from cell infusion. There was a significant difference in terms of the number of cells delivered (205 million BMCs vs 22 million CPCs), although there was a similar difference in cell number in TOPCARE-AMI. The disparate findings of these two studies suggest that while CPCs may be of benefit in the acute phase following infarction, they are not of benefit in the chronic phase, or may require a much higher dose to be effective. The biology of the acutely and chronically infracted heart is significantly different, and it is conceivable that CPCs might be suitable for treatment of one condition, and not the other. BMCs, on the other hand, contain a mixed population of cells, including CPCs and MSCs, which may make them more capable of effecting repair in the chronically injured heart. In any case, the results of TOPCARE-CHD have tempered enthusiasm for the use of CPCs in patients with chronic ischemic cardiomyopathy.

Apart from the treatment of LV dysfunction, CPCs have also been investigated for the treatment of refractory angina. In a study reported by Losordo et al., 24 patients with severe angina despite optimal medical treatment and without options for revascularization were randomized to receive endomyocardial injection of escalating doses of autologous CPCs or placebo.[46] The injections were performed using a NOGA Myostar injection catheter that allowed for targeting of cell delivery using electrical activity of the myocardium to delineate areas of scar in conjunction with traditional fluoroscopy. This delivery method was found to be safe, and patients receiving EPCs had some improvement in both qualitative and quantitative measures of angina severity, though no significant differences were found. The lack of a significant difference was attributed to the small sample size.

In all, these results suggest that although CPCs (or EPCs) have potential application in the treatment of both acute MI and chronic angina, they do not appear to be of benefit in chronic ischemic cardiomyopathy, and there are questions about their relative effectiveness compared with BMCs. It remains to be seen whether CPCs might prove beneficial in disorders specifically of the vasculature, an area of study that is being actively pursued.

## Cardiac-Derived Stem Cells

Since resident CSCs was first reported by Piero Anversa and colleagues,[2,3] several studies in preclinical animal models have confirmed the existence of these cells and demonstrated their ability to regenerate myocardial tissue when returned to the heart after ex vivo expansion.[4,5,47] Although CSCs exist in the adult heart, they do so in relatively small numbers compared with the myocardium as a whole, and appear to be primarily responsible for routine cell turnover. They are activated by, and multiply in response to, injury to the heart, but resident CSCs do not appear able to repair large insults de novo. Isolation and ex vivo expansion of CSCs, at least in theory, would allow for large, potentially therapeutic numbers of cells to be grown and returned to the heart to treat dysfunction. Like other forms of cell therapy for the heart, CSCs delivered to the heart may effect repair both directly, by forming new cardiac tissue, and indirectly, by enhancing the function of endogenous, resident stem cells through the production of paracrine factors.[48,49] The predetermined cardiac fate of CSCs may make them more effective than hematopoietic stem cells in forming new cardiac tissue, but their relative effectiveness has yet to be compared.

Initially, there was uncertainty as to which combination of surface marker expression constituted a "true" CSC, but it is now generally accepted that one such marker is c-kit, the surface receptor for stem cell factor. Two methods have been employed to isolate and expand these cells. The first, employed by Anversa and colleagues, selects and expands only those cells that express c-kit. This technique results

in a uniform, clonogenic population of cells, but due to the relatively low density of c-kit+ cells in the heart, it requires harvesting a large amount of cardiac tissue to allow for culture and expansion of a therapeutically relevant number of cells. A different method involves propogation of a heterogenous population of cells, a portion of which are c-kit+. Called "cardiosphere-derived cells," or CDCs, these cells may be routinely isolated from endomyocardial biopsy samples (typically 5–10 mg), obtained using a minimally invasive percutaneous bioptome.[5,47,52] Cardiosphere-derived cells are derived from "cardiospheres," free-floating spherical clusters of undifferentiated cells, which may be generated from biopsied heart tissue. These CDCs feature a subpopulation of c-kit+ cells (~10–20 percent), as well as ones expressing markers typical of MSCs, and may be rapidly expanded to large numbers in culture.

Using the c-kit+ selective method to obtain CSCs, Beltrami et al. first showed that cells isolated from the adult rat heart could differentiate into the three main cardiac cell types, namely: cardiac myocytes, vascular smooth muscle, and endothelial cells.[3] When injected at the infarct border zone in rats, CSCs regenerated myocardial tissue within the infarct and border zones, resulting in reduced infarct size, limited adverse remodeling, and improved ejection fraction and contractility compared with placebo-treated animals.

The isolation and therapeutic use of CDCs were first reported in 2004, when it was demonstrated that CDCs delivered to the hearts of mice after MI formed new, functional cardiac tissue.[5] Further work reported by Eduardo Marbán and his group[47] showed that CDCs can be isolated from routine human endomyocardial biopsy specimens, and grown to large numbers in vitro. When these cells were delivered to immunodeficient mice with acute MI, the delivered CDCs formed all three cardiac cell lines, regenerated cardiac tissue within the infarct border zone, and preserved LVEF as compared with animals treated with placebo (using both the delivery solution and human fibroblast cells for controls). Subsequent study in large animals showed that CDCs delivered to the heart by intracoronary infusion 4 weeks after MI engrafted and formed mature cardiac myocytes and vascular cells (see Fig. 53-3), and compared with placebo, reduced relative infarct size and improved hemodynamic function.[30]

The results of these preclinical experiments prompted phase I clinical trials using both c-kit-selected CSCs and CDCs for the treatment of ischemic cardiomyopathy. In the Cardiac Stem Cell Infusion in Patients with Ischemic Cardiomyopathy (SCIPIO) trial, patients with ischemic cardiomyopathy undergoing coronary artery bypass grafting (CABG) received intracoronary infusion of autologous CSCs isolated from the right atrial appendage, which is surgically resected at the time of CABG. In the Cardiosphere-Derived Autologous Stem Cells to Reverse Ventricular Dysfunction (CADUCEUS) study, patients suffering a recent MI with significant LV dysfunction (LVEF 25–45 percent) underwent percutaneous endomyocardial biopsy, from which

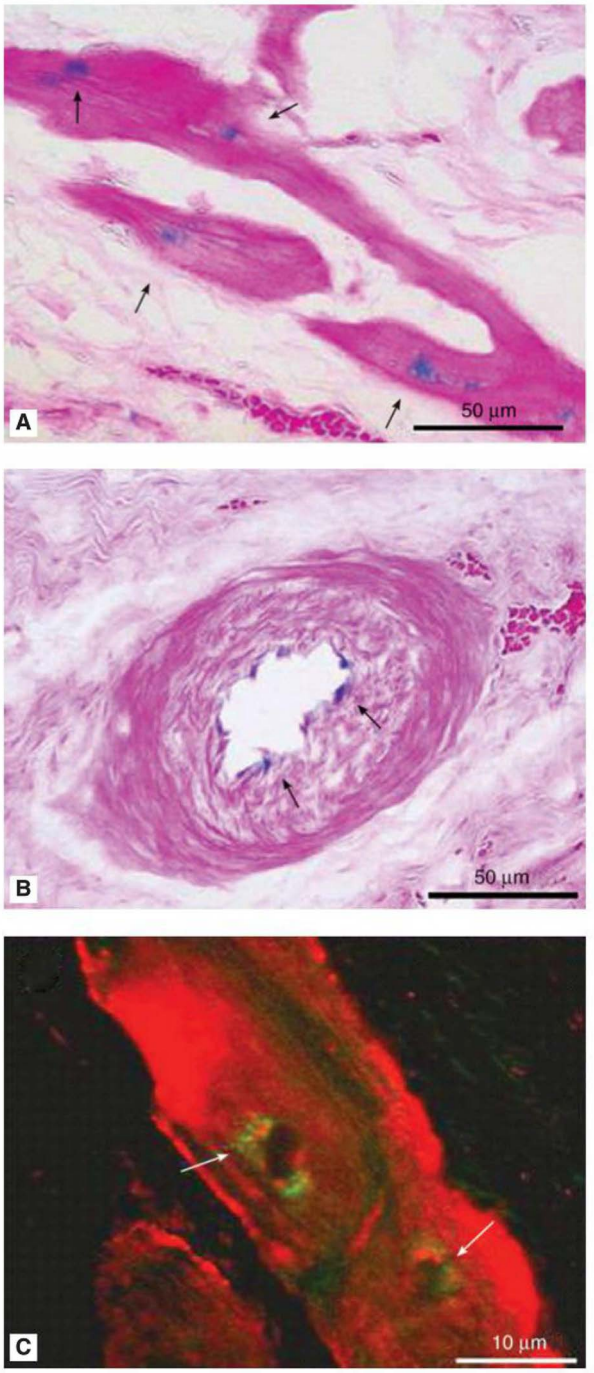



**FIGURE 53-3** Histopathologic slides of tissues taken from infarct border zone of pigs 8 weeks after intracoronary infusion of LacZ-labeled autologous cardiosphere-derived cells (CDCs) showing CDC engraftment, survival, and differention. In panel **A**, multiple mature cardiac myocytes with X-gal+ nuclei (arrows) are seen at the infarct border zone. In panel **B**, X-gal+ cells are incorporated in an arteriole at infarct border zone (arrows). Panel **C** shows immunohistochemical staining of the infarct border zone revealing adjacent cardiac myocytes with β-galactosidase+ nuclei (green) and expression of α-sarcomeric actin (red), indicative of a mature phenotype.

CDCs were isolated and later returned to the heart using intracoronary infusion. Both studies completed enrollment and reported positive results[50,51] that are expected to lead to phase II trials.

It should be noted that in contrast to the majority of trials using BMCs and MSCs, in the current trials of CSCs, patients receive cells weeks to months after the initial insult, in the subacute to chronic phase after infarction. This delay is in large part necessitated by the time required to isolate and expand autologous CSCs. If CSCs prove clinically effective at this time point, they will hold much promise for the treatment of those with chronic LV dysfunction, but one could also envision a treatment strategy for the treatment of acute MI with significant LV dysfunction in which such patients receive BMCs or MSCs in the acute phase, and those with residual dysfunction would later receive CSCs.

Although the majority of studies using CSCs focused on the heart damage caused by infarction, the concept of a population of resident CSCs responsible for routine repair and cell turnover has led to the concept that depletion or alteration of a patient's CSCs might result in cardiac dysfunction, and in turn, whether repletion of the CSC pool might reverse that dysfunction. In proof of this concept, De Angelis et al. published a study of a rat model of anthracycline-induced cardiomyopathy. In this study, treatment with syngeneic CSCs after the development of cardiomyopathy preserved LV function and limited adverse remodeling compared with placebo-treated animals.[53] If these results are confirmed, one could envision a treatment strategy in which patients undergoing a known cardiotoxic chemotherapy might "bank" autologous CSCs for therapeutic use in the event they develop cardiac dysfunction.

In summary, although it was once thought that the heart was incapable of repair, it is now known that a population of stem cells resides in the heart. In animal studies these cells have shown benefit for the treatment of both ischemic and nonischemic LV dysfunction. The clinical benefit of CSCs and relative effects of these cells compared with bone marrow–derived populations remain to be determined, but the mere recognition of the existence of resident stem cells in the heart presents an opportunity for the development of new therapeutic paradigms.

## Other Cell Types

### SKELETAL MYOBLASTS

Skeletal myoblasts offer a cautionary note in the use of progenitor cells for treatment of heart disease. One of the first types of cells used in clinical trials for the treatment of ischemic LV dysfunction, the theoretical advantages included the use of autologous cells, the ability to form large numbers, and resistance to hypoxia. The effects of direct epicardial injection of myoblasts at the time of surgery for CABG were examined in the MAGIC trial. In this trial skeletal myoblasts not only failed to significantly alter regional or global measures of LV systolic function compared with placebo, but were associated with a significantly higher rate of serious ventricular arrhythmias.[42] The latter finding could be explained by different electrical activation and coupling required of cardiac myocytes as compared with that of skeletal muscle cells; nevertheless, the realization that cell therapy could result in life-threatening arrhythmias gave the field pause.[41] This adverse outcome has instructed subsequent clinical trials of stem cell therapy for the heart, in which close monitoring for cardiac arrhythmias is imperative. To date, the use of BMCs and CSCs have not been found to be arrhythmogenic, and, as mentioned above, in at least one study MSC therapy reduced arrhythmias, an unexpected and reassuring finding.

### EMBRYONIC STEM CELLS

Embryonic stem cells (ESC), in theory, hold significant promise for the treatment of heart disease. Their clinical use has been limited, by reports that when used in animal models de novo, without differentiation or modification, injected ESCs can result in teratoma formation.[54] Using techniques to direct ESC differentiation along a cardiac pathway prior to delivery to the heart may eliminate this problem; however, further basic investigation is necessary before preclinical or clinical studies are performed. Induced pluripotent stem cells, created by genetic modification of fully differentiated adult cells, present another exciting source of potential cell therapy for the heart, though they have undergone only limited study at this point.

# STEM CELL DELIVERY METHODS

In addition to questions about which type of stem cell might be optimal for treatment of heart disease, a number of delivery methods have been studied, and the best remains to be determined. Techniques that have been used clinically include intracoronary infusion, epicardial injection (during surgery), endocardial injection (using catheter-based techniques), and intravenous infusion. In animal models, all of these techniques have been employed, as well as novel methods, employing gel or tissue matrices applied to the epicardium during surgery. The relative benefits and limitations of these delivery methods will be discussed below.

## Intracoronary Infusion

Of the delivery methods used to date, intracoronary infusion has been used most commonly.[8,10,11,13,19] Advantages of the intracoronary delivery method, whether using a standard angioplasty balloon catheter, or a specially designed catheter, include that it is minimally invasive, selective, and widely available clinically. In contrast to catheter-based endocardial injection, intracoronary infusion could be performed in a clinical cardiac catheterization laboratory,

utilizing techniques familiar to any interventional cardiologist. For these reasons, intracoronary infusion is the technique employed in most clinical studies of stem cell therapy for the heart. The major limitation of intracoronary infusion is that, at least when used in animal studies, intracoronary infusion of large numbers of cells has been at times complicated by vascular congestion and resultant infarction. For example, in preclinical animal experiments using miniature swine, intracoronary infusion of more than 300,000 CDCs/kg body weight was associated with raised troponin levels.[52] This extrapolates to approximately 30 million cells for the typical human subject (70 kg), which is far less than the 200–300 million BMCs that can be delivered by intracoronary infusion without reported complication in studies such as REPAIR-AMI and TOPCARE-CHD.[10,11] The difference is likely due to the diameter of these cell types: although BMCs have a typical diameter of 5–10 μm in suspension, CDCs and MSCs have a diameter of approximately 20 μm,[55] which is larger than the typical capillary lumen diameter of 7–10 μm. Another theoretical limitation of intracoronary infusion is that entry of cells into the myocardium requires crossing the vessel wall and tracking to the area of injury. Vascular permeability and the signals available to help stem cells track may be drastically affected by the stage of tissue injury and relative level of inflammation. Also, although large cells may clog the capillaries, a significant portion of smaller cells, due to their size, may pass directly from the arterial to venous network without ever coming in close enough contact with the vascular wall to enter the myocardium. Despite these potential limitations, the appeal of intracoronary infusion lies in its relative ease and wide clinical availability, and it is a technique that has proved effective in preclinical and some clinical studies to date.

## Epicardial Injection

Direct myocardial injection, via either the epicardium or the endocardium, has been widely employed in clinical trials as well. Epicardial injection during open heart surgery allows for visualization of the area of injury and exact targeting of the injections.[32,42] In addition, a potentially unlimited number of cells, regardless of size, can be delivered by this method. The obvious limitation, however, is that this technique, at least as it is currently employed, requires open chest surgery, a level of procedural invasiveness that in most cases is not felt to be justified for delivery of cell therapy alone. To date, epicardial stem cell injections have been performed only at the time of regularly scheduled surgery, most commonly during CABG. With the use of less invasive surgical methods, perhaps with thoracoscopic or robotic techniques, epicardial cell delivery may be performed in a less invasive manner that could make cell delivery alone an acceptable purpose for the procedure. Recent advances in epicardial mapping and ablation of ventricular arrhythmias using catheters placed in the pericardial space may also lead to methods by which catheter-based epicardial injections could be performed.

## Endocardial Injection

Endocardial cell injection has been performed using various catheter-based systems in a number of clinical trials.[46,56] These catheters are advanced to the left ventricle retrograde through the aortic valve using vascular access typical of interventional cardiology procedures. The Biosense NOGA system allows for electromechanical mapping of the ventricle prior to injection to delineate areas of scar and allow for targeted cell delivery.[46] Information gathered during the electromechanical mapping can be used with anatomic information from cardiac CT or MRI to provide even more precise targeting of injections. The Biosense system, however, is expensive, and is not available in the typical catheterization laboratory; its use therefore requires a substantial institutional commitment to cell therapy.

Other endocardial injection catheters do not require a dedicated mapping system, and instead use widely available fluoroscopic equipment. The Biocardia Helical Infusion System, for example, employs a deflectable guide catheter to advance a spiral-shaped injection needle to the endocardial wall (see Fig. 53-4).[56] Once in contact, the needle is rotated so that it advances into the myocardial wall similar to an active fixation pacemaker lead. After the injection is complete, the needle is rotated in the opposite direction to remove it from the wall. A possible advantage of this system is that by temporarily fixing the needle well into the myocardium, there is greater retention of the cell suspension as compared with a traditional straight needle. This, and other endocardial injection catheters, must be used cautiously, however, as myocardium scarred and thinned by prior infarction may be susceptible to perforation. Case selection is therefore critical to safe cell delivery by this method.

## Intravenous Infusion

Intravenous infusion is the least invasive technique used to date to deliver stem cells. The limited invasiveness of this technique must be balanced, however, with reduced delivery precision, as animal studies show that the majority of stem cells infused by this technique are retained in the lungs.[57,58] Nevertheless, hematopoietic stem cells are able to target areas of inflammation and injury, and the results of the PROCHYMAL study (described above) suggest there is potential benefit to intravenous infusion of MSCs within 10 days of a MI.[40] It remains to be determined whether the positive results seen in PROCHYMAL were primarily the result of MSCs targeting to and entering the area of myocardial damage. In addition, it is unclear whether such therapy would be beneficial in the setting of chronic ischemic cardiomyopathy, or nonischemic cardiomyopathy, in which an acute injury signal is not present and stem cell trafficking to the heart may be limited.

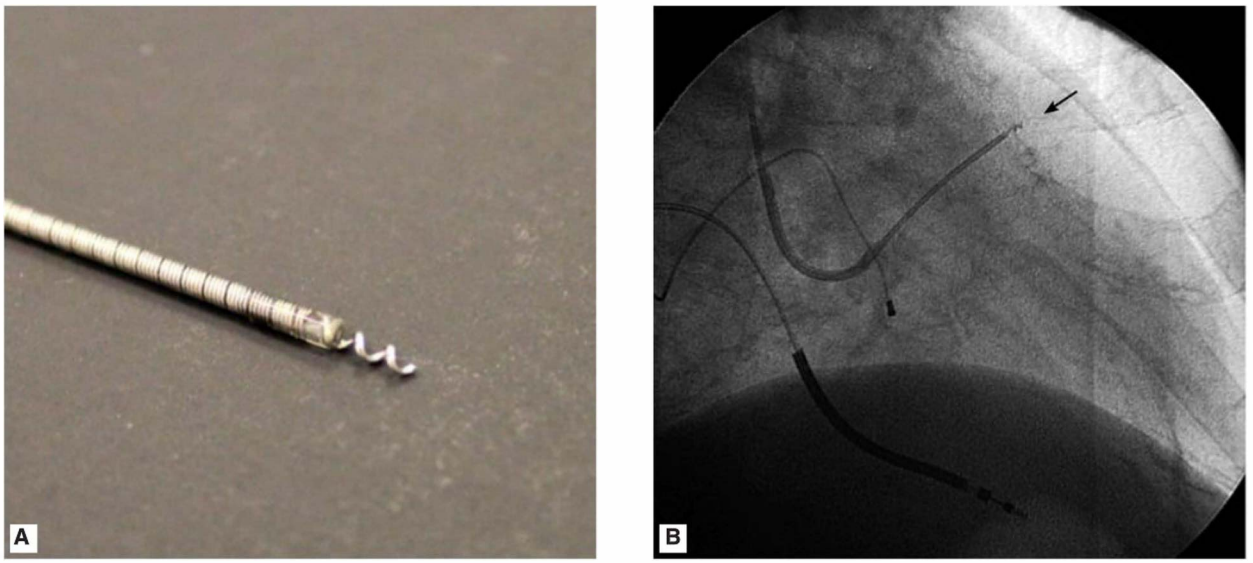



**FIGURE 53-4** The Biocardia Helical Injection Catheter (Biocardia, Inc, San Carlos, CA) is designed for endocardial delivery using percutaneous techniques. On contact with the endocardium, the helical needle at the end of the catheter (panel **A**) is rotated, advancing into the tissue and allowing for temporary fixation during cell infusion. Panel **B** shows the catheter advanced to the anterior wall for stem cell delivery in a patient with severe LV dilation and dysfunction.

## QUESTIONS AND FUTURE DIRECTIONS FOR CARDIAC STEM CELL THERAPY

As described above, stem cell therapy for the heart, with the exception of skeletal myoblasts, is safe, though the measured clinical effects on LV function remain modest to date. The failure to achieve the more robust benefits seen in animal models may reflect the complex nature of heart disease in adult humans, who most often have other comorbid conditions, and therefore may not respond in the same way to cell therapy as an otherwise healthy laboratory animal with experimentally induced cardiac dysfunction. Along the same lines, it remains to be determined whether, in cases where autologous stem cells are used, all stem cells are equally beneficial. For example, are the cardiac-derived stem cells obtained from an 80-year-old patient with diabetes and renal failure as efficacious clinically as those of a 48-year-old with premature coronary disease who is otherwise healthy? Furthermore, in cases where allogeneic cells might be used, might it be better to receive cells from a healthy 18-year-old donor as opposed to the patient with LV dysfunction? Although the cells of all patients may not have equal therapeutic efficacy, are there genetic or other modifications that could improve cellular efficacy?

Beyond the cells themselves, findings from the REPAIR-AMI trial and others suggest that certain patients benefit more than others from cell therapy, and point to unanswered questions about the optimal timing of cell therapy after injury. Perhaps most compelling is the finding across multiple studies that those patients with the greatest degree of LV dysfunction after MI benefit the most from cell therapy. This suggests that cell therapy can fill an unmet clinical need, and that the overall modest results to date may in part be due to dilution of studies with patients who have minimal LV dysfunction and therefore do not stand to benefit from cell therapy. The challenge going forward is finding ways to identify those patients that truly stand to benefit from cell therapy and focus study on these patients.

Finally, the results of multiple studies, both clinical and preclinical, suggest that although cell therapy can be efficacious, the benefit of cell therapy for the heart may not be the direct result of the cells themselves, but instead the paracrine factors and other signals the cells produce. The theoretical advantage of cell therapy is that delivered cells can adapt and respond to their environment in a manner far more complex than our current understanding. Regardless of whether it is ultimately understood that stem cells themselves are critical to generate adequate tissue repair, or only the factors they produce, the burden of cardiovascular disease warrants continued efforts to explore this new therapeutic modality.

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## STEM CELLS FOR CARDIAC SURGICAL DISEASE BOARD REVIEW QUESTIONS (CHAPTER 53)

1. How many Americans are estimated to have congestive heart failure?

   A. 100,000
   B. 500,000
   C. 6,000,000
   D. 10,000,000
   E. 50,000,000

2. Which of the following stem cell lines have been used in clinical trials for treatment of cardiac disease?

   A. Mesenchymal stem cells
   B. BMCs
   C. EPCs
   D. Skeletal myoblasts
   E. All of the above

3. Based on the findings of the REPAIR-AMI trial of BMCs in patients with an acute myocardial infarction, which of the following patients would be expected to have the greatest improvement in LVEF from BMC-therapy compared with placebo?

   A. Baseline LVEF 30 percent, cells given within 12 h of infarction
   B. Baseline LVEF 30 percent, cells given 1 day after infarction
   C. Baseline LVEF 30 percent, cells given 6 days after infarction
   D. Baseline LVEF 55 percent, cells given 1 day after infarction
   E. Baseline LVEF 55 percent, cells given 6 days after infarction

4. Which of the following types of stem cells has been associated with an increased rate of cardiac arrhythmias in clinical study?

   A. Mesenchymal stem cells
   B. BMCs
   C. Skeletal myoblasts
   D. Cardiac-derived stem cells
   E. Embryonic stem cells

5. Which of the following cell delivery techniques has been used most often in clinical trials of stem cell delivery to the heart?

   A. Intracoronary infusion
   B. Epicardial injection
   C. Intravenous infusion
   D. Endocardial injection
   E. Coronary sinus infusion

## ANSWERS

1. **Answer: C.** The American Heart Association estimates that nearly 6 million Americans suffer from congestive heart failure, about 2 percent of the total population.
2. **Answer: E.** Mesenchymal stem cells were used in the Safety Study of Adult Mesenchymal Stem Cells to Treat Myocardial Infarction study. BMCs were used in REPAIR-AMI and numerous other studies. Endothelial progenitor cells, or CPCs, were used in TOPCARE-CHD. Cardiac stem cells are being used in the SCIPIO and CADUCEUS trials.
3. **Answer: C.** In the REPAIR-AMI trial, those patients with significant LV dysfunction who received BMC infusion longer from the time of MI (6 days or greater) had a greater likelihood of significant improvement.
4. **Answer: C.** In the MAGIC trial, epicardial injection of skeletal myoblasts was associated with an increased rate of arrhythmias compared with placebo.
5. **Answer: A.** Due to the ease of use, minimal invasiveness, and wide clinical availability, intracoronary infusion has been used most often to deliver stem cells to the heart in clinical trials.

54

# Minimally Invasive Cardiac Surgery

*D. Kalavrouziotis*
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**KEY CONCEPTS**

- Innovations in alternative methods for cannulation and cardiopulmonary bypass (CPB), new visualization systems, retractors and stabilizers, and robotic platforms have facilitated the development of minimally invasive cardiac surgery.
- Minimally invasive direct coronary artery bypass (MIDCAB) and totally endoscopic coronary artery bypass grafting (TECAB) remain hindered by inherent technical complexities.
- Minimally invasive approaches for mitral valve surgery include mini-right thoracotomy, partial sternotomy, parasternal approach, and robotic port access.
- Complications associated with the endoclamp include balloon migration/rupture and retrograde aortic dissection.
- Elevated atherosclerotic plaques greater than 2 mm in height in the descending thoracic aorta or arch may increase the risk of retrograde cerebral and other systemic embolization and constitutes a contraindication to femoral artery-perfused minimally invasive mitral valve surgery.
- Relative contraindications for a mini-right thoracotomy mitral approach include previous right thoracotomy with dense pleural adhesions, significant obesity, severe chest deformity (e.g., pectus excavatum), scoliosis, and prior breast implant or reconstruction.
- Other operations that can be performed through a small right thoracotomy include tricuspid valve surgery, atrial septal defect closure, atrial myxoma resection, and septal myectomy.
- Minimally invasive approaches for aortic valve surgery generally consist of limited sternotomies.

The midline sternotomy incision offers excellent access to all cardiac structures and has been the traditional route for the performance of most cardiac operations. However, the growth and advancement of percutaneous interventional techniques such as coronary artery stenting have been accompanied by a growing patient willingness to undergo procedures with less favorable mid- and long-term outcomes compared with coronary artery bypass grafting (CABG), largely to enjoy lower periprocedural risks and less invasiveness. In response to this, cardiac surgeons have progressively developed less invasive operations to provide the benefits of standard cardiac procedures with less morbidity. Through the use of innovative surgical approaches combined with new technology, cardiac surgeons have introduced a spectrum of novel, minimally invasive operations. The avoidance of cardiopulmonary bypass (CPB) and/or the full median sternotomy incision are the main features common to this new generation of procedures. This chapter describes and discusses the evolution and results of minimally invasive cardiac surgery, with an emphasis on minimally invasive mitral valve operations.

## MINIMALLY INVASIVE CORONARY ARTERY BYPASS GRAFTING

Although the first attempts to revascularize ischemic myocardium were accomplished on a beating heart, the advent of CPB with cardioplegic arrest offered a reliable and highly reproducible means to perform CABG. During the mid-1990s, in an attempt to circumvent the need for sternotomy, surgeons developed a procedure to create a left internal mammary artery (LIMA)-to-left anterior descending coronary artery (LAD) anastomosis through a small left anterior thoracotomy. In this procedure, termed minimally invasive direct coronary artery bypass (MIDCAB), the LIMA

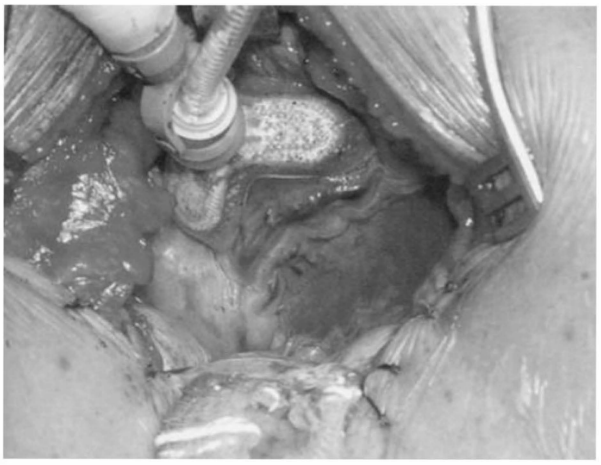


**FIGURE 54-1** Exposure and stabilization of right coronary artery (RCA) and posterior descending artery (PDA) using EndoStarfish via a transabdominal approach. (Reproduced with permission from Subramanian VA, Patel NU, Patel NC, et al. Robotic assisted multivessel minimally invasive direct coronary artery bypass with port-access stabilization and cardiac positioning: Paving the way for outpatient coronary surgery? *Ann Thorac Surg* 2005;79(5):1590–1596. Copyright Elsevier.)

is harvested through a left anterior thoracotomy or limited sternal split incision with the assistance of a variety of chest retractors. A stabilizer is subsequently applied on the beating heart, thus facilitating the performance of the coronary anastomosis (Fig. 54-1). Coronary occlusion is obtained proximally by snaring the coronary artery with a Silastic tape. Early experiences reported good graft patency rates.[1,2] In a meta-analysis including 17 studies of over 4000 patients, Kettering reported early and late mortality rates of 1.3 and 3.2 percent, respectively.[3] Conversion to sternotomy or CPB was 1.8 percent. At 6 months of follow-up, 3.6 percent of the 445 grafts that were studied angiographically were occluded; 7.2 percent had significant stenosis. Decreased postoperative pulmonary dysfunction and atrial fibrillation, as well as better pain management and quality of life indices have also been reported in patients undergoing MIDCAB.[4–6] MIDCAB procedures have also been applied with success to coronary reoperations.[7] Despite the purported advantages of MIDCAB, these minimally invasive procedures remain technically more challenging and require longer operative times with a higher rate of anastomotic revision compared with LIMA-to-LAD anastomoses performed through a standard sternotomy.[8,9] Furthermore, wound complications including incisional hernia, wound dehiscence or infection, and chronic pain, have been reported in up to 9.1 percent of patients.[10] Such wound complications, which are often a source of significant morbidity, are mainly linked to the excessive rib spreading required to harvest the LIMA through a limited thoracotomy. To minimize wound complications, surgeons developed a procedure to harvest the LIMA with a standard thoracoscope, thus minimizing rib spreading.[11]

Multivessel disease is also amenable to minimally invasive approaches without the use of CPB. The LIMA can be harvested and all myocardial territories can be revascularized via a small left anterolateral thoracotomy, with additional stab incisions made for the introduction of epicardial stabilizers and apical positioners. Proximal anastomoses are constructed either to the LIMA or to the ascending aorta using a proximal connector or direct suture after application of a side-biting clamp. A recent two-center consecutive series of 450 patients, including 7 patients with previous CABG, demonstrated acceptable procedural outcomes, with a 1.3 percent mortality rate, conversion to sternotomy in 3.8 percent, use of CPB in 7.6 percent, stroke in 2 patients (0.4 percent), and thoracic wound infection in 1 patient (0.2 percent).[12] However, these were a highly selected group of patients, with three-vessel disease present in only 28.4 percent of patients; 73.8 percent received only one or two grafts. All 34 patients requiring CPB received a graft to the circumflex coronary system. At a mean follow-up of 19 months, 3 percent of patients required percutaneous coronary intervention, mainly related to problems with the proximal LIMA T-graft anastomosis.

## TOTALLY ENDOSCOPIC CORONARY ARTERY BYPASS (TECAB)

Several dedicated centers have actively pursued the development of robot-assisted totally endoscopic coronary artery bypass grafting (TECAB) on the beating and arrested heart. The first successful TECAB on a human arrested heart was performed by Loulmet and colleagues in 1998.[13] With this approach, the LIMA is harvested, femoro-femoral CPB is initiated, and the heart is arrested by occluding the ascending aorta with an endovascular balloon and infusing cardioplegic solution into the aortic root. The LIMA-to-LAD anastomosis is performed in a running fashion using robotic instrumentation passed into the chest via modified thoracoscopic ports.

Despite its initial success, TECAB is associated with significant technical limitations. First, aortic cross-clamp and CPB times are usually much greater than with standard techniques.[14] Second, the duration of LIMA harvest is significantly prolonged and LIMA injury can occur in up to 6 percent of patients.[15] Third, the procedure is generally limited to single-vessel bypass of the LAD, although successful multivessel robot-assisted operations have also been reported.[16] In experienced hands, conversion rates to sternotomy or larger thoracic incisions are less than 10 percent. In one study, graft patency was 100 percent at discharge among the 22 out of 45 patients with predischarge angiograms.[17] Furthermore, recently published 5-year clinical outcomes in 100 patients demonstrate greater than 90 percent survival and freedom from angina.[18] However, multicenter randomized controlled data are needed to better define the role of TECAB in the current management of patients with coronary artery disease, especially given the higher prevalence of multivessel and diffuse disease, diabetes, previous percutaneous coronary intervention, and higher urgency in contemporary surgical cohorts. To ensure

a safer and more reliable operation, further technological refinements are needed. Improvements in imaging technologies, telemanipulation systems, and endoscopic stabilizers will optimize surgical exposure and anastomotic construction. Direct suturing of the coronary anastomosis remains difficult and time-consuming. Development of distal anastomotic devices may facilitate the performance of TECAB anastomoses on the beating heart. However, variations in patient anatomy, such as intramyocardial LAD or excessive epicardial fat, significantly limit the applicability of these techniques. In such circumstances, the use of endoscopic ultrasound or other imaging modalities may prove useful for the accurate identification of coronary vessels. Although the current literature supports the feasibility of TECAB on the beating or arrested heart using computer-assisted surgical robotic systems, cost issues, limited clinical indications, and a steep learning curve currently limit the widespread use of this technology. Robot-assisted minimally invasive coronary artery bypass surgery remains in its evolutionary stage. Its success will be predicated on a methodical approach, combining improvements in both technology and in surgical techniques.

## MINIMALLY INVASIVE MITRAL VALVE OPERATIONS

The era of mitral valve surgery began with the treatment of severe mitral stenosis by closed commissurotomy.[19] However, it was not until the development of the heart–lung machine in 1953 that direct access to the mitral valve became possible. Commissurotomy was then performed under controlled direct vision through a left or right atriotomy. Development of a replacement prosthesis for valves not amenable to repair progressed rapidly after the first mitral valve replacement performed in 1961 by Starr and Edwards.[20] The complications encountered with valve replacement with a prosthesis led surgeons to investigate alternative techniques to repair the mitral valve. The establishment of a physiologic classification system of mitral valve disease by Carpentier in the 1970s allowed for a systematic approach to repair the mitral valve.[21] Further developments in prosthetic rings ensured reproducible and durable mitral valve repairs.[22] With refinements in both operative technique and perioperative patient management, mitral repair surgery through a sternal approach can now be performed with mortality rates ranging from 1 to 4 percent with minimal morbidity.[23,24] Furthermore, freedom from reoperation after mitral repair is excellent, especially when the disease is localized to the posterior leaflet and the postoperative echocardiogram shows minimal residual mitral regurgitation.

## EVOLUTION IN MINIMALLY INVASIVE MITRAL SURGERY TECHNIQUES

Although right lateral thoracotomy with femoral cannulation was utilized to expose the mitral valve during the early days of open cardiac surgery, standard sternotomy became the preferred method to access the mitral valve. During the mid-1990s, efforts to avoid a midline sternotomy led to the development of alternate ways to expose the mitral valve. The Cleveland Clinic group initially advocated a parasternal approach but then shifted to an upper midline partial sternotomy. Using this technique, Cosgrove and colleagues reported results similar to a standard sternotomy.[25] Other partial sternotomy incisions have also been described, such as the subxiphoid approach consisting of a transverse skin incision overlying the xiphoid process with an inverted J-type mini-sternotomy.[26] Advantages of these approaches include central cannulation for CPB as well as good valve exposure. However, the need for sternal division is not obviated and incisions are less esthetically pleasing to patients when compared with the right mini-thoracotomy incision.

During the same time period, other surgeons revisited the right lateral thoracotomy approach to expose the mitral valve. Initial work demonstrated that the mitral valve could be accessed and operations adequately performed through a small right thoracotomy incision.[27] Experimental work by the Stanford group led to the development of the Port-Access Endo-CPB system.[28] This platform utilizes peripheral cannulation through the femoral vessels for CPB (Fig. 54-2). A branched femoral arterial cannula allows insertion of an endovascular balloon catheter which is positioned in the ascending aorta. Aortic occlusion is performed by inflating the balloon and cardioplegia may be administered through the distal lumen of the catheter. A percutaneous retrograde cardioplegia catheter was also developed and is positioned in the coronary sinus through a right internal jugular venous puncture (Fig. 54-3). Similarly, a venting catheter may be percutaneously positioned in the main pulmonary artery to ensure a bloodless operative field. The mitral valve is exposed using specialized left atrial retractors. Clinical studies performed with the Port-Access system (Edwards Lifesciences, Irvine, CA, USA) demonstrated the feasibility of the procedure.[29] However, device-specific complications such as endoclamp-induced retrograde aortic dissection led to further modification of the technique. In 1997, Chitwood introduced a percutaneous transthoracic aortic clamp (Fig. 54-4A), thus eliminating use of the endoclamp and its attendant potential risks such as balloon migration, rupture, and retrograde aortic dissection.[30] To enhance mitral valve visualization during the procedure, other groups have proposed the use of two-dimensional video endoscopes.[31] Robotic approaches involving the da Vinci system (Intuitive Surgical, Inc., Sunnyvale, CA, USA) have also emerged with good short- and midterm outcomes (Fig. 54-5).[32]

Throughout the development of the right mini-thoracotomy technique, the establishment of dedicated teams was recognized as a prerequisite to a successful outcome. Anesthesiology expertise in transesophageal echocardiography is of paramount importance for percutaneous catheter positioning. Effective communication between team members during the various steps of the operation is essential. Furthermore, perfusionists need to be facile in the management of novel CPB techniques to ensure optimal

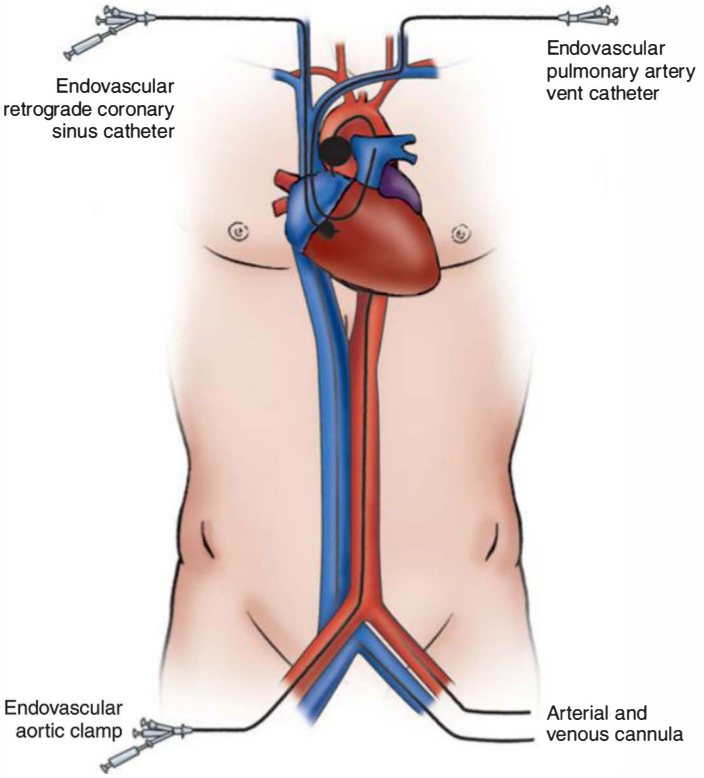



**FIGURE 54-2** Schematic diagram of the Port-Access EndoCPB system. The venous and arterial cannulas are connected to the bypass pump. The endovascular aortic clamp is inserted through the femoral artery. The pulmonary artery vent is inserted through the left jugular vein, and the percutaneous venting catheter is inserted through the right jugular vein. (Reproduced with permission from Schwartz DS, Ribakove GH, Grossi EA, et al. Minimally invasive mitral valve replacement: Port-Access technique, feasibility, and myocardial functional preservation. *J Thorac Cardiovasc Surg* 1997;113(6):1022–1030. Copyright Elsevier.)

functioning of the Port-Access platform and a smooth conduct of the operation.

Currently, most centers favor the right lateral minithoracotomy approach for minimally invasive mitral valve operations. CPB is instituted through cannulation of the femoral vessels. Long-shafted specialized instruments are used for mitral valve manipulation (Fig. 54-4B). Although the majority of centers tend to avoid using the endovascular aortic clamp, its use has been proven to be safe in high-volume centers well-experienced in this technique.[33] Conversely, the Chitwood clamp adopted by numerous groups, has been shown to be safe and effective and requires



**FIGURE 54-3** Percutaneous retrograde cardioplegia catheter.

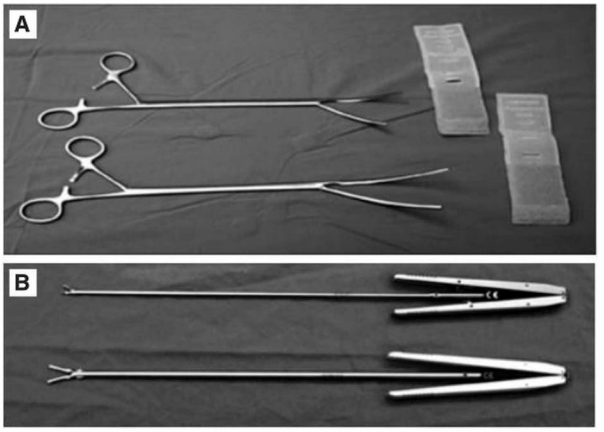



**FIGURE 54-4** Chitwood transthoracic aortic clamps (**A**) and long-shafted instruments (**B**) used in minimally invasive mitral valve surgery.



FIGURE 54-5 The da Vinci surgical robotic system. This system consists of a "slave" robotic platform controlled by the surgeon, who sits at a "master" console equipped with manual actuators a nd a dual-camera stereoscopic optical system. (Photograph courtesy of Intuitive Surgical, Sunnyvale, CA.)

less aortic manipulation. Although cardioplegia may be administered by direct needle puncture of the ascending aorta, the use of a percutaneously inserted coronary sinus catheter for retrograde cardioplegia as well as percutaneous pulmonary artery catheterization for left ventricular venting facilitate exposure by allowing for a bloodless operative field without the presence of cumbersome catheters in the limited work space (Fig. 54-6).

## PATIENT SELECTION

Indications for minimally invasive mitral valve surgery are similar to those that are in effect during conventional mitral surgery through a median sternotomy. However, patient-related factors may influence the decision to proceed with a minimally invasive approach. For example, when considering retrograde aortic perfusion through the femoral artery during CPB, the presence of elevated atherosclerotic plaques >2 mm in height in the descending thoracic aorta or arch may increase the risk of retrograde cerebral and other systemic embolization and constitutes a contraindication to femoral artery-perfused minimally invasive mitral valve surgery. The surgeon must then evaluate alternative arterial cannulation sites or, if not available, resort to a conventional median sternotomy. Other relative contraindications are the presence of significant obesity, a previous right thoracotomy with dense pleural adhesions, a severe chest deformity such as a pectus excavatum or severe scoliosis, and previous breast implant or reconstruction. In our center, over 80 percent of patients referred for an elective isolated mitral valve operation are candidates for a right mini-thoracotomy. The principles of mitral valve replacement and repair during minimally invasive exposure of the mitral valve are no different than those that



FIGURE 54-6 View of a completed mitral valve repair through a limited right thoracotomy.

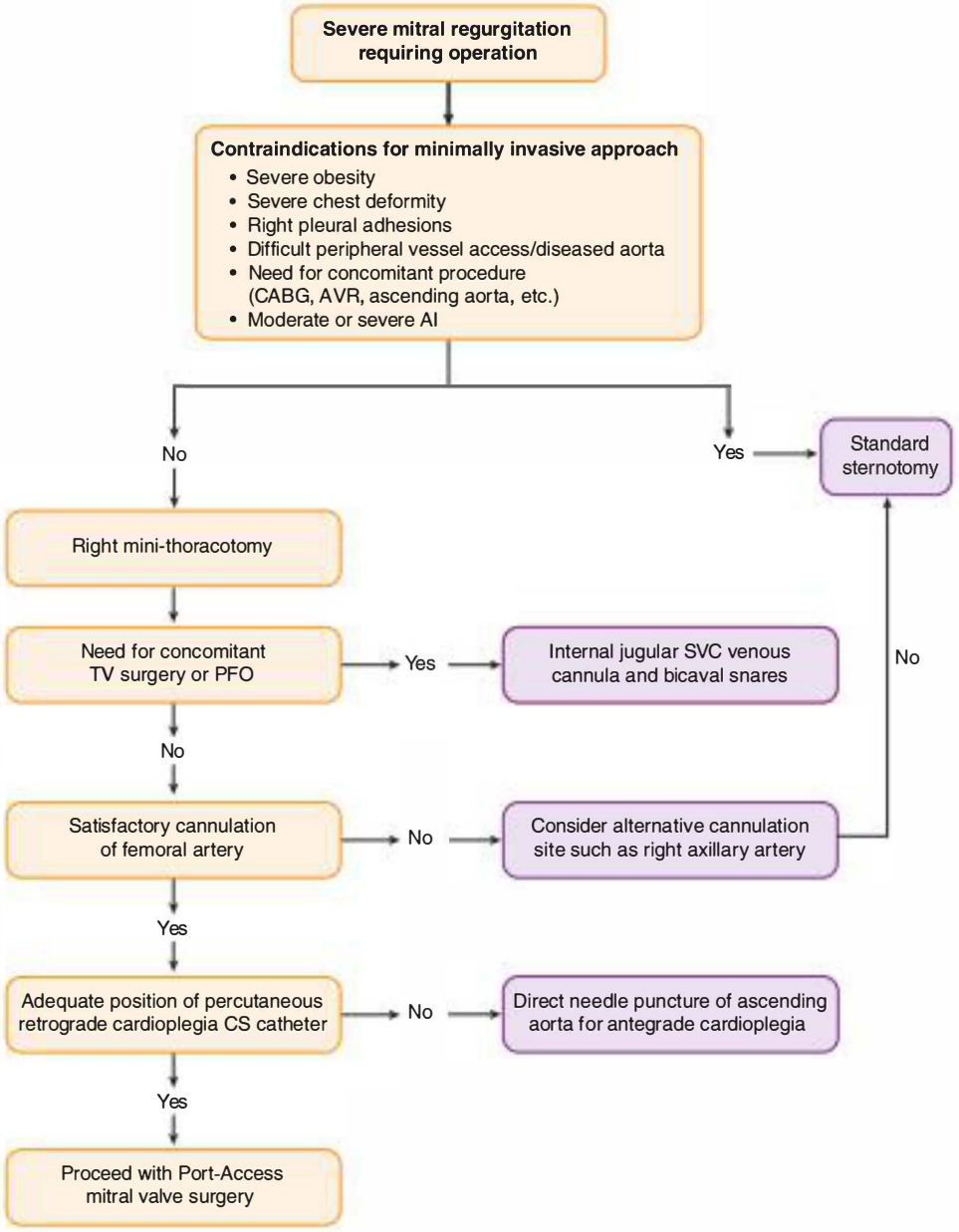



**FIGURE 54-7** Decision-making flowchart used during minimally invasive mitral valve surgery. AI, aortic insufficiency; AVR, aortic valve replacement; CABG, coronary artery bypass graft surgery; CS, coronary sinus; PFO, patent foramen ovale; SVC, superior vena cava; TV, tricuspid valve.

are now well-established in mitral surgery by standard sternotomy. A decision-making flowchart is shown in (Fig. 54-7).

## SURGICAL TECHNIQUE

At the Quebec Heart and Lung Institute, Quebec City, Canada, minimally invasive mitral valve surgery through a right mini-thoracotomy has been performed since 2003. Our technique has been standardized as follows. Following general anesthesia and endotracheal intubation, a retrograde cardioplegia coronary sinus catheter and a pulmonary artery venting catheter are inserted through the right internal jugular vein. Positioning of the coronary sinus catheter is guided by transesophageal echocardiography and fluoroscopy. A bronchial blocker is placed in the right mainstem bronchus to deflate the right lung, thus minimizing lung trauma during the procedure. The right side

of the thorax is elevated 30° from the operating table and a 3- to 5-cm fifth intercostal space right lateral mini-thoracotomy is performed. Soft-tissue and intercostal retractors are placed with care being taken not to over-spread the ribs to minimize postoperative pain and thoracic splinting. The pleural cavity is flooded with $CO_2$ to facilitate de-airing of the cardiac chambers. The femoral vessels are exposed through a 2- to 3-cm incision in the inguinal fold. A 22F or 25F venous cannula (Edwards Lifesciences, Inc., Irvine, CA, USA) is inserted in the common femoral vein with its distal tip positioned in the superior vena cava under echocardiographic guidance. A 20F-to-22F arterial cannula (DLP; Medtronic, Inc., Minneapolis, MN, USA) is inserted through the common femoral artery. CPB with mild passive hypothermia is then instituted with vacuum-assisted venous drainage. The aorta is clamped using a Chitwood transthoracic clamp inserted in the third intercostal space and myocardial protection is achieved with intermittent retrograde cardioplegia via the balloon-inflatable coronary sinus catheter every 15 to 20 min. Exposure of the mitral valve is performed through Sondergaard's groove and specialized left atrial retractors are placed. Visualization of the mitral valve and subvalvular apparatus is assisted by video thoracoscopy. The operation then proceeds as in standard mitral valve approaches.

**TABLE 54-1: Preoperative Characteristics of Patients that Underwent Mitral Valve Surgery by Right Mini-thoracotomy ($n$ = 173)**

| Preoperative Variables (% Unless Otherwise Indicated) | |
|---|---|
| Age (mean years ± SD) | 58.1 ± 11.7 |
| Female | 32.9 |
| Active cigarette smoking | 12.7 |
| Body mass index[a] (mean ± SD) | 25.2 ± 3.9 |
| Diabetes mellitus | 6.4 |
| Hypertension | 39.9 |
| Peripheral vascular disease | 2.3 |
| Previous stroke | 4.6 |
| Left ventricular ejection fraction <0.40 | 1.2 |
| NYHA class III–IV | 37.6 |
| Previous myocardial infarction | 6.9 |
| Atrial fibrillation | 47.4 |
| Pulmonary hypertension | 18.1 |
| Previous cardiac surgery | 8.1 |
| Renal failure (serum creatinine >150 µmol/L)[b] | 3.5 |
| Chronic obstructive pulmonary disease | 9.8 |

NYHA, New York Heart Association; SD, standard deviation.

[a]Body mass index = weight in kg/(height in m)$^2$.

[b]Serum creatinine > 1.7 mg/dL.

## RESULTS

Although a small, randomized clinical trial demonstrated the feasibility of minimally invasive mitral valve surgery,[34] no large, well-powered clinical trial has compared this approach to standard sternotomy with respect to clinical outcomes, durability of repair, and markers of patient satisfaction. Moreover, considering the growing global interest in the technique and an increasing patient recognition of the availability of minimally invasive approaches, such a trial may be difficult to perform. Therefore, available data on minimally invasive mitral valve surgery rely mainly on prospective observational single-center experiences. At the Quebec Heart and Lung Institute, 173 mitral valve procedures have been consecutively performed since 2003 using the right mini-thoracotomy Port-Access technique described above. The mean age of patients was 58 ± 12 years, and 33 percent were female. Most patients had normal left ventricular function, and approximately 40 percent of patients were in NYHA class III–IV (Table 54-1). Operative variables and in-hospital outcomes are shown in Table 54-2. Conversion to sternotomy was required in four patients (2.3 percent). There was one in-hospital mortality due to mesenteric ischemia, and two patients required reoperation for failed repair, one at 2 weeks and the other at 4 weeks following the initial operation. At a mean follow-up of 2.5 ± 1.5 years, 1-, 2-, and 5-year survival rates were 98.0, 96.4, and 94.4 percent, respectively. Midterm freedom from mitral valve reoperation is also excellent, 99.4 percent at 5 years.

Similar results using the right mini-thoracotomy approach have been reported by other groups.[35–38] Interestingly, renal complications appear to be less frequent with the right mini-thoracotomy approach.[39,40] Enhanced renal preservation may be related to increased renal perfusion associated with femoral artery cannulation during CPB. Although complications directly related to sternal incisions are eliminated, the surgeon must be aware of specific complications related to the minimally invasive approach that are not commonly observed with standard mitral valve surgery via sternotomy. Phrenic nerve injury, parenchymal lung trauma, and perioperative pleural effusion may be minimized by intraoperative right lung exclusion and extended pleural drainage for a minimum of 3 days. Transesophageal echocardiographic guidance has reduced the incidence of peripheral vessel complications to less than 1 percent during cannulation. In a large, single-center series, the incidence of aortic injury attributed to the use of the endoclamp was 0.9 percent, resulting in a mortality rate of 22.2 percent.[33] Coronary sinus trauma owing to percutaneous retrograde catheterization is less than 2 percent with the use of fluoroscopy during catheter positioning. However, in our experience, it may be impossible to achieve adequate positioning of the percutaneous coronary sinus catheter in up to 20 percent of cases, necessitating alternative cardioplegia delivery approaches.

To assess the rate and durability of valve repair in patients with degenerative mitral valve disease, we prospectively evaluated 36 patients with degenerative disease operated on through a right mini-thoracotomy at our center. Posterior

**TABLE 54-2: Operative Variables and In-hospital Outcomes of Patients that Underwent Mitral Valve Surgery by Right Mini-thoracotomy ($n = 173$)**

| Variables (% Unless Otherwise Indicated) | |
|---|---|
| *Operative characteristics* | |
| Urgent operation | 4.0 |
| Aortic occlusion time (mean minutes ± SD) | 93.1 ± 29.4 |
| Cardiopulmonary bypass time (mean minutes ± SD) | 119.5 ± 37.3 |
| Pure mitral stenosis | 11.0 |
| Etiology of MV disease | |
| Myxomatous degeneration | 70.5 |
| Rheumatic | 19.7 |
| Endocarditis | 2.9 |
| Ischemic | 2.3 |
| Failed previous repair | 1.2 |
| Concomitant MAZE | 30.6 |
| Concomitant tricuspid valve surgery | 3.5 |
| Mitral valve operation | |
| Replacement | 45.1 |
| Repair | 54.9 |
| Conversion to sternotomy | 2.3 |
| *In-hospital outcomes* | |
| Mortality | 0.6 |
| TIA-stroke | 3.5 |
| New-onset atrial fibrillation | 12.7 |
| Low cardiac output syndrome | 2.3 |
| Mechanical ventilation >48 h | 2.9 |
| Reoperation for bleeding | 4.0 |
| Renal failure[a] | 2.3 |
| Length of hospital stay (mean days ± SD) | 7.1 ± 3.1 |

MV, mitral valve; SD, standard deviation.

[a]Increase in serum creatinine of greater than 50 μmol/L.

leaflet prolapse was present in 22 patients, the anterior leaflet was involved in 2 patients, and bi-leaflet prolapse occurred in 12 patients. Thirty-three patients (91.7 percent) underwent mitral valve repair using conventional repair techniques with immediate postoperative transesophageal echocardiography showing no or trace residual mitral regurgitation. At a mean follow-up of 12.8 ± 8.4 months, all patients had stable repairs except for one patient who required reoperation for recurrent severe mitral regurgitation due to an early postoperative *Streptococcus mitis* endocarditis. Similar valve repair rates and outcomes were reported by other groups.[41–43]

Patient satisfaction and quality of life seem to be improved with the minimally invasive approach. Pain levels are usually well-tolerated with the common medications in current use during the initial postoperative days. Following the third postoperative day, pain level scores are significantly lower following right mini-thoracotomy compared with standard sternotomy.[44] Early mobilization is also improved. Following hospital discharge, patients do not face the same limitations to physical activity as those that have undergone sternotomy, and usually resume their normal activities within a month of the operation. Furthermore,



**FIGURE 54-8** Typical incision length in a patient that has undergone a right mini-thoracotomy.

patients appreciate the excellent cosmetic result afforded by the right mini-thoracotomy incision, which allows for a smaller visible scar without compromising the safety and efficacy of the procedure (Fig. 54-8). Costs of the procedure may be increased by US$3000 to US$7000 depending on the Port-Access catheters used during the operation. However, the potential reduction in length of hospital stay, the improvement in quality of life, and a more expeditious return to work may enhance the overall cost-effectiveness of the right mini-thoracotomy approach.

## EXTENDED APPLICATIONS AND FUTURE PERSPECTIVES

With slight modifications in technique, tricuspid valve surgery combined with a mitral valve procedure may be performed through a right mini-thoracotomy approach. Other procedures such as closure of an atrial septal defect, resection of atrial myxoma, and septal myectomy have also been reported using a small right thoracotomy. Exposure via a right mini-thoracotomy may also be a favorable option in cases of previous sternotomy especially in the presence of patent coronary artery bypass grafts. Although benefits have yet to be uniformly established, initial results are promising in patients with previous sternotomy.[45] In a series of 80 patients undergoing reoperative mitral or tricuspid valve surgery via a minimally invasive technique, Casselman and colleagues report an operative mortality of 3.8 percent and an incidence of stroke of 2.5 percent.[46]

The use of telemanipulators has been proposed by Chitwood in the early 2000s.[47] This procedure uses the da Vinci system in which the mitral valve operation is performed totally endoscopically. Feasibility of the procedure has been demonstrated by the Chitwood group and others.[48] However, CPB times are significantly prolonged and the current prosthesis technology still requires a 3-to-5-cm

thoracotomy. Furthermore, high purchase and maintenance costs of the robotic system may be prohibitive and most centers have not adopted this technique. In the near future, progress in stentless prosthesis technology may render this approach more appealing.

## MINIMALLY INVASIVE AORTIC VALVE SURGERY

The quest to reduce patient morbidity from cardiac operations led surgeons to develop approaches to avoid a complete sternotomy in performing aortic valve surgery. Various surgical incisions have been proposed, including an inverted "T" partial upper sternotomy, "J" upper partial sternotomy, "I" sternotomy performed between the second and fifth intercostal spaces, midline lower-half sternotomy, and a "C" mini-sternotomy, leaving the upper and lower ends of the sternum intact.[49–51] Right parasternal approaches have also been described, with or without resection of costal cartilages. All of these approaches permit central cannulation and good exposure of the left ventricular outflow track, aortic valve, and ascending aorta. Cardioplegia is usually administered in an antegrade fashion. A retrograde coronary sinus catheter may be directly inserted through the right atrium or percutaneously through the internal jugular vein. Continuous carbon dioxide is infused into the mediastinum to minimize the risk of air embolization after aortic unclamping. Following the initiation of CPB, the aortic valve operation is conducted using standard techniques.

Procedural mortality appears to be similar between minimally invasive aortic valve procedures compared to the conventional median sternotomy approach,[52,53] although no large, well-conducted randomized trial exists. Excellent results have also been reported in redo cases with patent coronary bypass grafts (Fig. 54-9).[54] Improved cosmesis, reduced duration of mechanical ventilation and length of hospital stay, and diminished postoperative pain with an earlier return to normal activity have been associated with the minimally invasive approach.[55,56] However, consistent reductions in blood product requirement, incidence of postoperative supraventricular tachyarrhythmias, and overall health care costs have been more difficult to demonstrate.

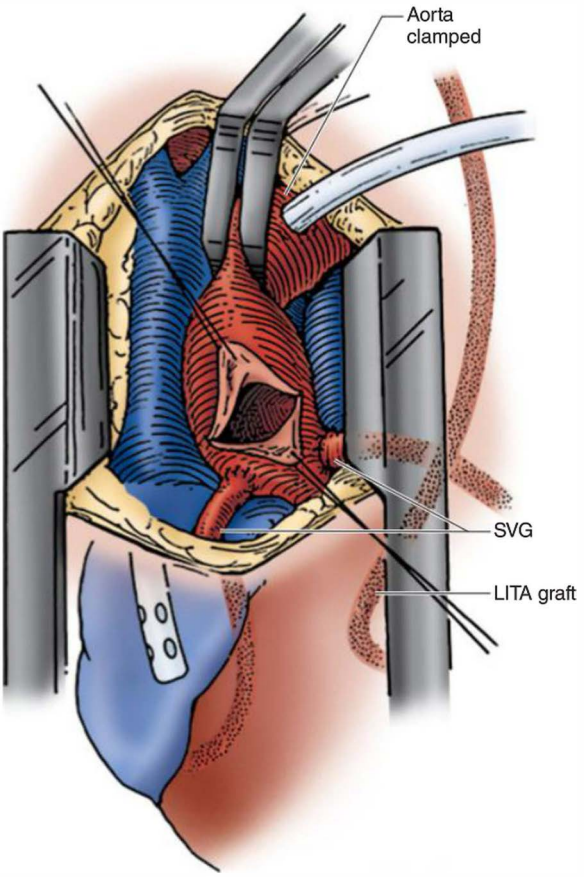



**FIGURE 54-9** Inverted "T" upper partial sternotomy approach to the aortic valve after prior coronary bypass. The previous sternotomy incision is exposed to the third (or fourth) intercostal space and extended laterally to the right or bilaterally, as needed, for exposure. After dissection of the ascending aorta, with particular attention to the position of patent CABG conduits and their proximal anastomoses, cannulation is performed. (In this example, the ascending aorta and innominate vein, but frequently other cannulation sites, are required because of space limitations.) The ascending aorta is cross-clamped and aortic valve replacement is conducted in standard fashion. LITA, left internal thoracic artery; SVG, saphenous vein graft. (Reproduced with permission from Byrne JG, Aranki SF, Couper GS, et al. Reoperative aortic valve replacement: Partial upper hemisternotomy versus conventional full sternotomy. *J Thorac Cardiovasc Surg* 1999;118(6):991–997. Copyright Elsevier.)

## OTHER MINIMALLY INVASIVE CARDIAC OPERATIONS

The acceleration of new technologies supporting minimally invasive cardiac surgery has encouraged surgeons to design new approaches to treat different cardiac diseases. Robotic surgery has been applied to correct some congenital defects, including coarctation of the aorta, atrial septal defects, and congenital mitral abnormalities.[57,58] With the combined development of new devices and innovative surgical techniques, the surgical treatment of atrial fibrillation ablation has seen a spectacular transformation from the classic time-consuming cut-and-sew Maze operations to fully robotic procedures for epicardial isolation of the pulmonary veins (Fig. 54-10).[59] Minimally invasive procedures have also been applied to epicardial biventricular lead placement, pericardial window, the excision of cardiac tumors, as well as transmyocardial laser revascularization.[60,61] Further research will be required to optimize patient selection for these types of procedures and determine the full benefits of these new operations.

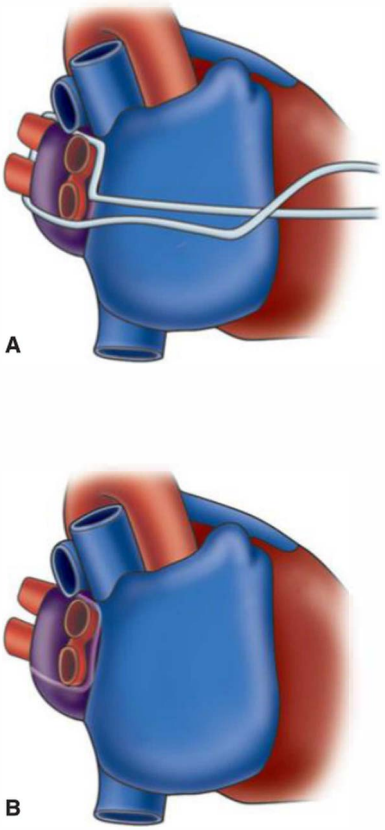



**FIGURE 54-10** Minimally invasive pulmonary vein isolation for atrial fibrillation. A flexible radiofrequency antenna is deployed around all four pulmonary veins via a minimally invasive technique (e.g., robotic right minithoracotomy). An isolating lesion is then created, thus ablating aberrant conduction pathways.

## CONCLUSIONS

During the last decade, innovations in alternative methods for cannulation and CPB, new visualization systems, retractors and stabilizers, and robotic platforms have paved the way for new and exciting developments in minimally invasive cardiac surgery. Compared with conventional surgical approaches, early experiences with minimally invasive valve surgery have produced excellent reproducible results in experienced centers with measurable benefits in the form of reduced perioperative morbidity and enhanced patient satisfaction. TECAB procedures remain hindered by the inherent technical complexities of the operation. Through further technological advancements and the development of new surgical strategies, TECAB procedures may be performed with more ease, safety, and reproducibility. Cardiac surgeons will apply these new technologies to other cardiac applications. Although this expensive technology is currently restricted to centers dedicated to minimally invasive approaches, technical refinements and evidence-based data confirming the benefits of these approaches should contribute to the widespread adoption of these techniques. To ensure the maintenance of the high standards set by conventional cardiac surgery, high-quality training programs in minimally invasive approaches will be required and will definitely constitute a challenge in the upcoming years.

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## MINIMALLY INVASIVE CARDIAC SURGERY BOARD REVIEW QUESTIONS (CHAPTER 54)

1. Which of the following is *not* associated with minimally invasive mitral surgery?
   A. Higher incidence of renal complications
   B. Coronary sinus injury
   C. Phrenic nerve injury
   D. Reduced cost
   E. Lung trauma

2. Peripheral cannulation is required for which of the following incisions for minimally invasive aortic valve surgery?
   A. "J" partial upper sternotomy
   B. Midline lower half sternotomy
   C. Inverted "T" upper half sternotomy
   D. Parasternal incision
   E. Peripheral cannulation is not required for any of these incisions.

3. Which of the following is correct regarding minimally invasive coronary artery bypass surgery?
   A. Early mortality exceeds 2 percent for MIDCAB.
   B. Less than 5 percent of MIDCAB LIMA-LAD grafts have significant stenosis at angiography.
   C. Anastomotic revision is less common with MIDCAB compared with standard CAB.
   D. Wound complications occur in nearly 10 percent of MIDCAB patients.
   E. Stroke is more common after multivessel minimally invasive CAB compared with standard CAB.

4. TECAB surgery is associated with:
   A. Requirement for CPB and arrested heart
   B. Prolonged cross-clamp and CPB times
   C. Conversion to open incisions in about 20 percent of patients
   D. Reduced midterm freedom from angina compared with standard CAB
   E. Ideally suited for intramyocardial LAD

5. Which of the following is the strongest contraindication to minimally invasive mitral valve surgery?
   A. Obesity
   B. Pectus excavatum
   C. Atherosclerotic plaque >2 mm in height in aortic arch
   D. Previous right thoracotomy
   E. Breast augmentation

## ANSWERS

1. **Answer: A.** An increased incidence of renal complications is not associated with minimally invasive mitral surgery; in fact, renal complications may be lower due to proximity of perfusion with femoral arterial cannulation. Coronary sinus injury, phrenic nerve injury, and lung trauma are all associated with cannulation, positioning, and exposure for minimally invasive mitral surgery through the right chest. Minimally invasive operations, in general, cost more than standard operations.
2. **Answer: E.** Central cannulation is possible with any of the incisions, and therefore peripheral cannulation is not absolutely required for minimally invasive aortic valve surgery.
3. **Answer: D.** Wound complications are common after MIDCAB operation, occurring in nearly 10 percent of patients. Early mortality is less than 2 percent. Both intraoperative anastomotic revision and residual postop stenoses are more common after MIDCAB. Stroke is not more common after multivessel minimally invasive CAB.
4. **Answer: B.** Totally endoscopic coronary artery bypass is associated with longer cross-clamp and CPB times. Recent advances have made TECAB surgery possible on the beating heart. Conversion to open incisions is uncommon in experienced hands. An intramyocardial LAD is a contraindication to TECAB.
5. **Answer: C.** Significant atherosclerotic disease in the aortic arch can represent high risk for embolization during minimally invasive mitral surgery, particularly if endoaortic balloon occlusion is required. The other conditions make the surgery more difficult but are not contraindications per se.

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# Cardiac Catheterization and Interventions

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## KEY CONCEPTS

- The most common complications of cardiac catheterization include groin complications (0.43 percent) such as hematomas, retroperitoneal bleeding, pseudoaneurysm, and arteriovenous fistulas. Other complications include contrast reactions, renal failure, perforation, dissection, hypotension, and bradycardia.
- When performing coronary angiography, at least two orthogonal views are needed for each vessel to assess the severity of eccentric lesions, and at least five views are recommended to adequately evaluate the left coronary system.
- By coronary angiography, a lesion is considered to be severe if there is a greater than 70 percent narrowing of the luminal diameter.
- For intermediate lesions of uncertain significance on coronary angiography, intravascular ultrasound (IVUS) and fractional flow reserve (FFR) can be useful. IVUS delineates and quantifies the atherosclerotic burden and consistently demonstrates that lesions are underestimated using angiography alone. FFR is probably the best test to determine both physiologic ischemia (i.e., disease severity) and the need for revascularization.
- Balloon angioplasty alone is associated with a 5 percent risk of abrupt closure and a 50 percent risk of angiographic restenosis within 6 months. Bare metal intracoronary stents decrease restenosis by nearly 50 percent compared to balloon angioplasty with a 20 to 30 percent risk of in-stent angiographic restenosis after 6 months.
- Drug-eluting intracoronary stents are associated with lower in-stent restenosis rates as low as 5 percent at 12 months, but also carry a higher risk of late and very late stent thrombosis. Patients receiving drug-eluting stents (DESs) must take aspirin for life and clopidogrel for at least 12 months after implantation to mitigate the risk of stent thrombosis.
- Cardiac output measurements can be obtained during right-heart catheterization by the Fick and/or thermodilution method. The thermodilution method is more accurate at high-output states, whereas the Fick method is more accurate with low-output conditions and atrial fibrillation.
- Aortic valve gradients can be estimated by several methods: (1) Peak-to-peak gradient, (2) "pull-back" method, and (3) simultaneous pressure measurements in the left ventricle (LV) and aorta using a double-lumen catheter (most accurate). The modified Hakki equation can be used to measure the aortic valve area: aortic valve area = cardiac output/square root of the peak-to-peak pressure gradient.
- Balloon aortic valvuloplasty (BAV) rarely increases aortic valve area greater than 1.0 $cm^2$ and, although it improves symptoms, clinical deterioration frequently occurs within 6 to 12 months.
- Percutaneous patent foramen ovale (PFO) closure devices are associated with high procedural success and low complication rates. Complication rates are around 5 percent and include device migration, pericardial tamponade, and arrhythmias.

## INDICATIONS FOR CARDIAC CATHETERIZATION

The first coronary angiogram was performed by Dr. F. Mason Sones, Jr. at the Cleveland Clinic in 1958, and he published the results of approximately 1000 procedures in 1962.[1] With the development of improved catheter designs by pioneers such as Drs. Kurt Amplatz and Melvin Judkins, the number of diagnostic cardiac catheterizations performed annually began to expand exponentially. The rapid growth of cardiac catheterization coincided with Dr. Rene Favaloro's introduction of coronary artery bypass grafting (CABG) in 1968.[1] Presently, almost 2 million cardiac catheterizations are performed each year in the United States.[1]

The most common indication for cardiac catheterization is the diagnosis of coronary artery disease (CAD). Accepted indications for cardiac catheterization include the evaluation for known or suspected CAD, chest pain, myocardial infarction (MI), wide complex tachycardia, cardiac arrest, shortness of breath, cardiomyopathy, valvular disease, congenital heart disease, aortic dissection, pericardial disease, and heart transplantation.[1] Coronary arteriography determines the severity of obstructive CAD and identifies other etiologies of ischemia and infarction, including thrombosis, spasm, dissection, and myocardial bridges.[1]

Cardiac catheterization plays an integral role in the evaluation and management of patients with cardiomyopathy and heart failure by quantifying the degree of left ventricular (LV) dysfunction with ventriculography and by measuring both right- and left-sided filling pressures. Cardiac catheterization differentiates systolic from diastolic dysfunction, distinguishes pericardial constriction from restriction, and determines the severity of valvular disease. In patients with valvular disease, left-heart catheterization is indicated when there is a disparity between echocardiographic and physical exam findings, and coronary angiography is recommended prior to valve surgery in patients greater than 35 years of age.[1]

Although there are no absolute contraindications for cardiac catheterization, there are several relative contraindications such as severe contrast allergy, coagulopathy (INR greater than 1.8), renal failure, gastrointestinal bleeding, electrolyte imbalance (hypokalemia and hyperkalemia), acute stroke, infection, fever, severe anemia, uncontrolled hypertension, decompensated heart failure, high-grade heart block, uncontrolled arrhythmias, thyrotoxicosis, and medication toxicity.[1]

Cardiac catheterization is safe even in critically ill patients, but indications for catheterization should always be based on the risk–benefit ratio.[1] Major complications infrequently occur during catheterization. According to an analysis of approximately 60,000 cases, death occurred in only 0.11 percent of patients, and patients with either severe aortic stenosis or critical left main (LM) disease were at the highest risk.[1] Incidence of MI, stroke, and arrhythmias is 0.05, 0.07, and 0.38 percent, respectively.[1] The most common complications of cardiac catheterization include groin complications (0.43 percent) such as hematomas, retroperitoneal bleeding, pseudoaneurysm, and arteriovenous fistulas.[1] Obesity, anticoagulation, female gender, and advanced age are associated with an increased incidence of vascular complications, especially when performed from a femoral artery access site.[1] Other complications of catheterization include contrast reactions, renal failure, perforation, dissection, hypotension, and bradycardia.

## BASIC CATHETERIZATION TECHNIQUES

Cardiac catheterization is an invasive procedure and should only be performed by well-trained clinicians who understand the basic fundamentals of catheterization. The patient must be NPO after midnight for 6 to 8 h prior to catheterization. It is imperative to establish continuous electrocardiogram (ECG) monitoring and intravenous (IV) access for the administration of sedation, fluids, and medications. Patients with a contrast allergy should be treated with prednisone and Benadryl, and IV fluids are administered to those at risk for contrast-nephropathy to achieve greater than 200 mL/h of urine output. Acetylcysteine (Mucomyst) is also frequently administered prior to angiography in individuals at risk for contrast dye nephrotoxicity, although the efficacy of this drug in preventing this remains unproven. A crash cart and defibrillator must be charged and readily available during the procedure.

After the patient is draped in a sterile fashion and comfortably sedated, percutaneous vascular access is most frequently achieved via cannulation of the right common femoral artery. The femoral artery crosses the inguinal ligament, which is located beneath the inguinal skin fold, and divides the ligament into two-thirds lateral and one-third medial.[2] Needle entry should be 1 to 3 cm below the inguinal ligament, and the inguinal skin crease should not be used as a landmark as it can be misleading, especially in obese patients.[3] After palpation of the femoral pulse, a hemostatic clamp is placed over the presumed access site and fluoroscopy should be performed to ensure that the puncture site will be 1 cm lateral to the medial edge of the middle of the femoral head in the anteroposterior projection (Fig. 55-1). This increases probability of an infrainguinal puncture and cannulation of the common femoral artery. A more cranial puncture increases risk of retroperitoneal bleeding, while cannulation below the bifurcation into the superficial femoral artery is associated with an increased likelihood of a pseudoaneurysm.[1] Next, local anesthesia using 1 percent lidocaine should be administered with a 25-gauge needle superficially and then a 22-gauge needle into the deep tissue planes. An 18-gauge beveled needle is introduced into the artery at a 30° to 45° angle resulting in pulsatile bleeding, and slight and careful manipulation of the needle (shallower angle) might be required to improve or restore flow. Single anterior wall puncture is preferred over the Seldinger double-wall technique, and many operators use a micropuncture kit to minimize groin complications.[2] After cannulation of the femoral artery, a soft J-tipped 0.035-in guide wire is

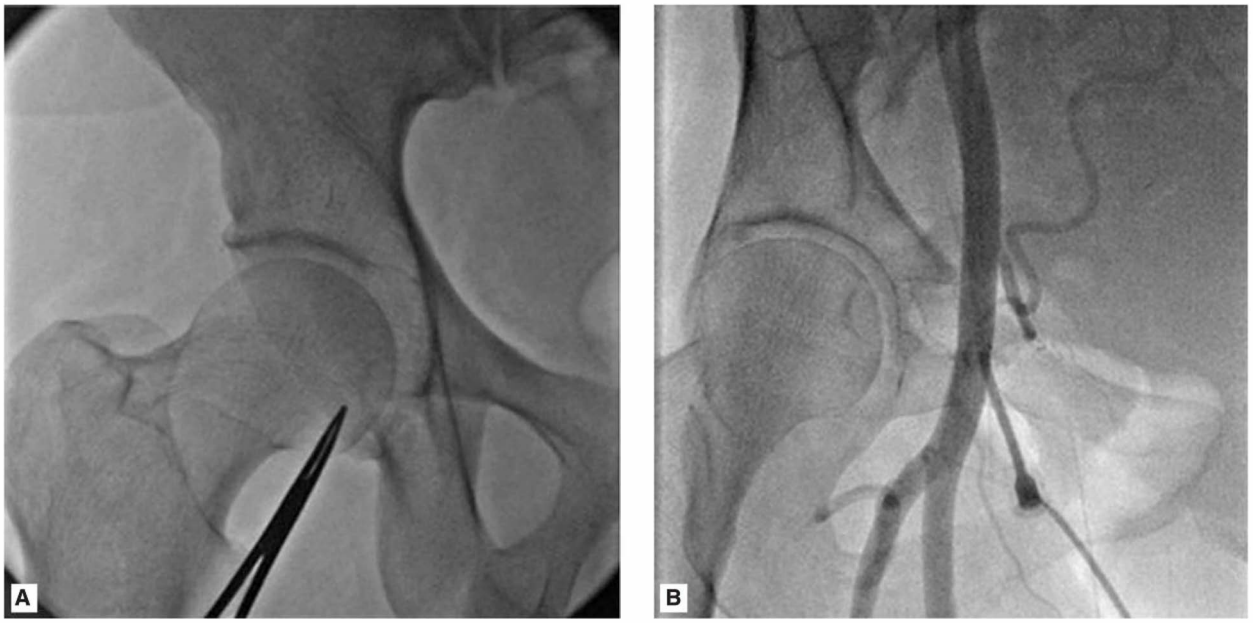



**FIGURE 55-1** **A.** The fluoroscopic landmark for access in the anteroposterior projection is approximately 1 cm lateral to the medial edge of the middle of the femoral head, which is marked by a hemostat. **B.** An iliofemoral angiogram in the right anterior oblique projection shows the sheath entering the right common femoral artery.

gently advanced through the needle and into the artery without resistance. If there is any resistance, the wire should be removed, and the needle should be repositioned if arterial flow is compromised. Hemostasis should be maintained for at least 2 to 3 min if the needle is withdrawn from the artery. Once the guide wire is easily passed through the needle, fluoroscopy is performed confirming wire placement in the abdominal aorta, which is left of the anatomic spine. At this point, the needle is removed, and typically a 5F or 6F sheath is inserted over the wire to ensure constant arterial access.

The most widely accepted technique for left-heart catheterization and coronary angiography is the Judkins method, which is associated with enhanced efficiency and low complication rates.[3] The LM coronary artery is usually engaged with the Judkins Left 4 (JL 4) catheter, while the Judkins Right 4 (JR 4) catheter is commonly selected for the right coronary artery (RCA). Engagement of the ostia is performed in the left anterior oblique (LAO) projection. In patients greater than 6 ft tall or in those with dilated aortic roots, a JL 5 or JL 6 may be necessary whereas a small aortic root might need a JL 3.5. Amplatz catheters are helpful when the ostia of the LM or RCA is more superior, anterior, or posterior than the typical aorta, but these catheters increase the risk of ostial dissection secondary to deep engagement.[3]

After coronary angiography, a pigtail catheter is introduced into the LV, and LV systolic and end-diastolic pressures are obtained. If the LV end-diastolic pressure is less than 30 mm Hg, left ventriculography is then performed in the 30° right anterior oblique (RAO) projection for a single-plane projection or 30° RAO and 60° LAO for biplane projection, using the pigtail catheter and a power injection of 30 mL of contrast media at 10 mL/s. A greater volume of contrast up to 60 mL or even 72 mL can be used if the LV is dilated or in the setting of chronic mitral regurgitation. The pigtail is then pulled back across the aortic valve while pressure is recorded on the hemodynamic monitoring system, and an aortic gradient is measured to assess for aortic stenosis. During catheterization, the patient's hemodynamics, oxygenation, ventilation, and level of consciousness must be continuously monitored. Once the catheterization is completed, the vascular sheath is removed, and hemostasis is achieved with manual compression for at least 10 to 15 min. Bed rest is mandatory for at least 3 to 4 h, and the patient must keep his or her leg straight to prevent hematoma.

Several vascular closure devices such as suture closure (Perclose, Abbott Laboratories, Abbott Park, Illinois), collagen plugs (Angio-Seal, St. Jude Medical, St. Paul, Minnesota), metallic clips, and hemostatic patches are available.[3] Closure devices minimize compression time, allow for early sheath removal in patients who have received anticoagulation, and enable patients to ambulate within 1 to 2 h following the procedure.[3] Prior to deployment, an iliofemoral angiogram must be performed in an oblique view to verify sheath entry above the femoral bifurcation (Fig. 55-1). Closure devices should not be used in patients with peripheral arterial disease, compromised immunity, or before valve surgery. A closure device is also discouraged if the vessel is less than 4 mm in diameter.[1] Although vascular access complications are probably not decreased with vascular closure devices they facilitate earlier ambulation and improve patient comfort. Use of vascular closure devices should be guided by proper patient selection and single anterior wall puncture.[4]

The femoral artery is the most common site of arterial access for cardiac catheterization, but brachial and radial arteries can also be used. Morbid obesity, severe debilitating back pain, peripheral claudication, previous femoral arterial grafting surgery, excessively tortuous aortic or iliac disease, femoral bruits, and absent lower extremity pulses are indications for selecting an alternative site for vascular access.[2] Radial artery access is more widely utilized outside of the United States for cardiac catheterization, but in light of studies demonstrating lower associated access site bleeding complications with radial compared to femoral access, there is increased interest in employing radial access in the United States.

Sones described the first cardiac catheterization using a brachial artery cutdown, but this technique is infrequently used today.[3] Rather, a percutaneous brachial artery technique is preferred without the need for cut down or repair.[3] The brachial artery should be cannulated several centimeters proximal to the elbow crease, because 10 percent of patients have a brachial bifurcation before the crease.[1] After a 4F to 6F sheath is introduced into the brachial artery, IV heparin should be given to prevent thrombus formation. Nitroglycerin is also recommended, because the brachial artery has the propensity for spasm. Advantages of using brachial over femoral arterial access include quicker time to ambulation and improved patient comfort.[3] Although it is easier to achieve hemostasis via the brachial approach, complication rates between brachial and femoral arterial access are indistinguishable.[3] Expanding hematomas and compression syndrome (forearm and hand) are more common after brachial access, because there is less space in the arm.[2] The brachial approach compromises image quality, increases radiation exposure, and impairs procedural efficiency as catheter manipulation can be quite challenging.[3] As a result, this technique should be reserved for patients who are not candidates for either femoral or radial access.[2]

Radial artery cannulation was first described by Campeau in 1989 and emerged as an alternative to the brachial approach in an effort to minimize vascular complications.[3,5] It has become increasingly popular to perform catheterization via the right radial artery secondary to markedly reduced time to ambulation and easier vessel compressibility, which controls bleeding.[1,2] In fact, patients may sit up and ambulate immediately after the procedure, facilitating outpatient cardiac catheterization.[3] Prior to cannulating the right radial artery, an Allen's test must be performed to verify dual circulation to the palmar arch. The left radial artery is frequently used as access for catheterization in the presence of a left internal mammary arterial (LIMA) graft. After the usual sterile prep and drape, the right radial site is locally anesthetized, and a 5F or 6F sheath is inserted into the radial artery using a micropuncture kit. Unfractionated heparin, intra-arterial nitroglycerin, and a nondihydropyridine calcium channel blocker should be administered to prevent thrombosis and vasospasm.

A recent meta-analysis of 12 randomized trials, including 3224 patients, showed that radial artery cannulation markedly decreased vascular complications, but it required greater technical skills and had slightly lower success rates.[5] Catheter manipulation from the wrist is more challenging than from the groin.[1] Other limitations of this approach include the small size of the radial artery, its increased likelihood for vasospasm, and the risk of radial artery occlusion from clot or dissection.[3] The radial approach increases the operator's exposure to radiation as the operator stands closer to the radiation source.[1] Radial artery access limits both guide selection and size if a complex percutaneous intervention is warranted, and an additional access site is often required if a right-heart catheterization is needed.[3] However, right-heart catheterization can be performed from the forearm with conversion of a peripheral IV catheter to a 6F sheath.

It is essential that the entire catheterization team be cognizant of the risks of radiation. Cumulative doses of radiation can result in skin erythema, hair loss, and necrosis, and these injuries occur in a dose dependent manner after a certain limit is exceeded (deterministic effects).[1,3] Radiation can also cause genetic defects and malignancies, and these feared complications of radiation are not dose dependent; rather, the probability of an effect is increased with radiation use (stochastic effects).[1,3] All catheterization personnel must understand the basic principles of minimizing radiation exposure. Radiation exposure is limited by the use of lead aprons, thyroid shields, and lead glasses. The catheterization table must have a lead shield to protect the operator's lower body and an adjustable glass lead shield for his or her upper torso and head. Radiation is also limited by reducing fluoroscopic and especially cineangiographic time, minimizing image magnification, and through the use of collimators (decrease field size) and less angled views.[6] Projections performed in the lateral, LAO, and steeply angulated caudal or cranial view increase radiation exposure to the patient and operator and are also associated with reduced image quality.[1] Minimizing distance between the patient and x-ray source reduces radiation exposure, and doubling the distance between the x-ray entrance and the operator decreases radiation dose to the operator by as much as 75 percent.[1] Catheterization personnel must wear radiation badges at all times; the maximum amount of whole body radiation dose per year and per lifetime is 5 and 50 rems, respectively.[3]

## CORONARY ANATOMY

The LM coronary artery arises from the left sinus of Valsava usually at an acute angle, and it travels between the left atrium and the pulmonary artery and is partially covered by the left atrial appendage.[7] The LM gives rise to the left anterior descending (LAD) artery, which supplies the anterior wall of the LV, and the left circumflex (LCx) artery, which supplies the lateral wall. In one-third of patients, the LM trifurcates into the LAD, ramus intermedius artery, and the LCx.[7] The ramus intermedius has a similar course as the first diagonal branch of the LAD and the first or high obtuse marginal branch of the LCx and provides blood supply to

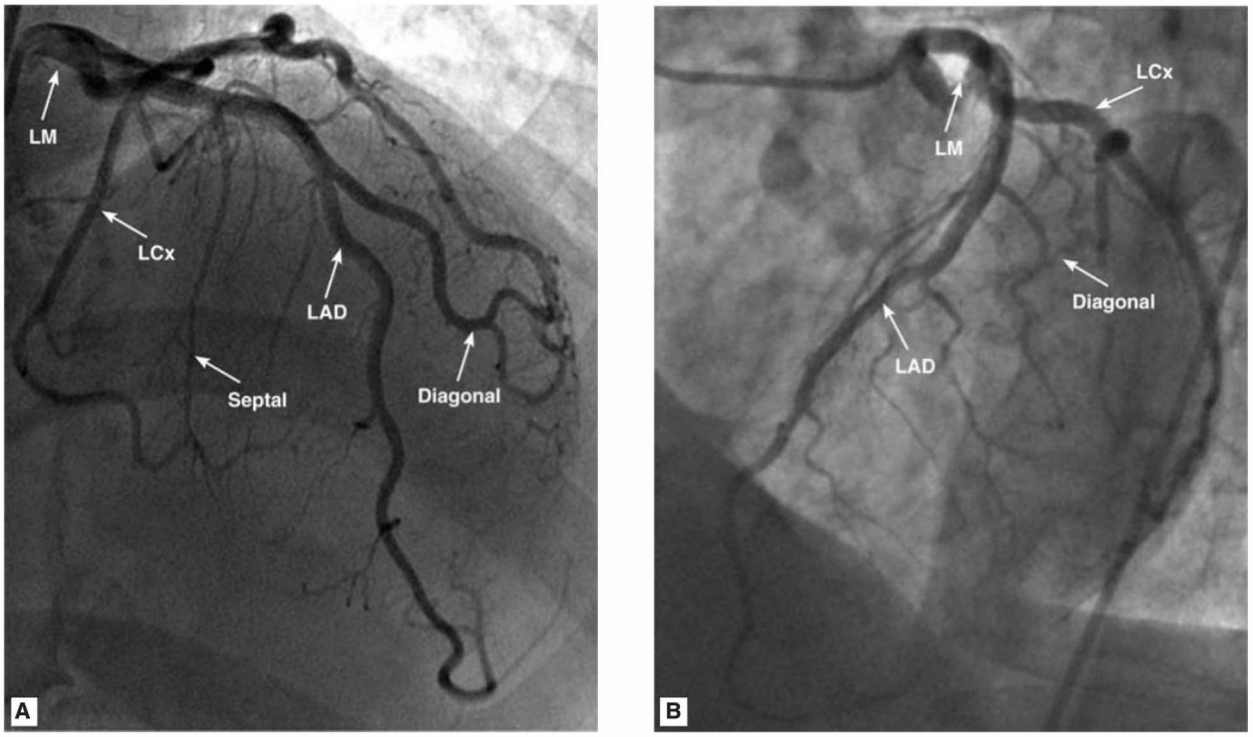



**FIGURE 55-2** **A.** The left system in the right anterior oblique cranial projection and the (**B**) left anterior oblique cranial view. LM, left main; LAD, left anterior descending; LCx, left circumflex.

the high lateral wall of the LV. The LAD gives off several diagonal and septal perforator branches as it courses along the anterior interventricular groove before either tapering into a small caliber vessel ending at the cardiac apex or wrapping around the apex to supply the distal one-third of the inferior wall (Fig. 55-2). The septal perforators supply two-thirds of the anterior portion of the interventricular septum and the majority of the conduction system including the His bundle.[8] The LAD diagonal branches supply the anterolateral aspect of the LV.[7]

The LAD takes an intramyocardial course in approximately 12 percent of patients,[7] and myocardial bridges almost always involve the mid-LAD but can infrequently affect a septal branch, the posterior descending artery (PDA), or an obtuse marginal branch. Bridging is easier to appreciate angiographically after administration of nitroglycerin.[1] Systolic narrowing of coronary arteries rarely causes ischemia as the majority of coronary flow occurs during diastole. Although myocardial bridging is benign in the majority of cases, it can result in critical luminal compression during systole in 2 percent of patients and also impair early diastolic coronary flow.[9] Myocardial bridging can make bypass surgery more challenging, especially during minimally invasive approaches.[1]

As the LCx courses along the left atrioventricular (AV) sulcus, it gives rise to small-caliber left atrial branches and several obtuse marginal branches, which supply the lateral wallbefore terminating in the AV groove (Fig. 55-3). The first obtuse marginal branch is frequently called the high lateral branch, and subsequent marginal branches may be referred to as left posterolateral branches.

The RCA originates from the right aortic sinus and supplies the inferior wall of the LV and right ventricle (RV). The first branch arising from the RCA is the conus branch. The proximal RCA then gives origin to small caliber right atrial branches and several acute marginal branches that supply the free wall of the RV.[7] In 85 percent of patients, the RCA is dominant and the distal RCA crosses the crux and bifurcates into the right posterior descending artery (RPDA) and right posterolateral ventricular (RPLV) branches distally (Fig. 55-4). The origin of the PDA defines coronary dominance as it determines the source of blood supply to the inferior wall of the LV, and it can arise from a dominant LCx in a minority of patients.[9] The length of the RCA along the inferior wall of the heart tends to be inversely related to the length of the LCx.[7] The inferior wall of the heart is supplied by both the RCA and the LCx in 20 percent of patients, and this is referred to as a mixed, shared, or codominant system.[7] The conus branch supplies the RV outflow tract and arises 50 percent of the time from a separate ostium in close proximity and anterior to the origin of the RCA.[1,9] Although the atrial branches of the RCA provide blood supply to the sinus

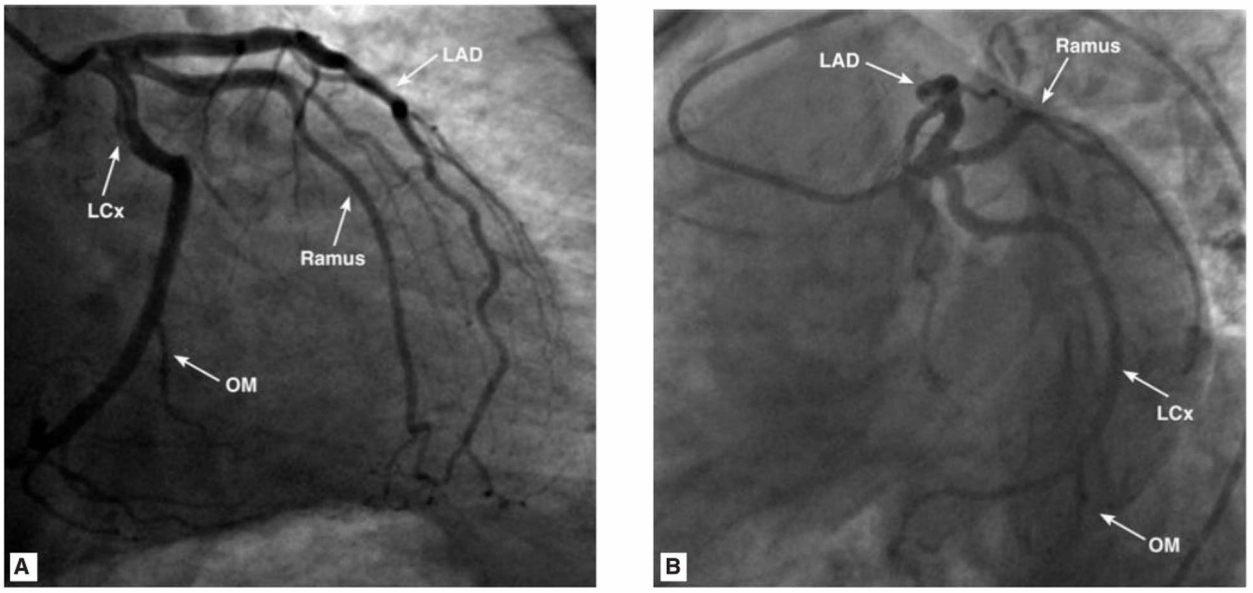



**FIGURE 55-3** **A.** The left system in the right anterior oblique caudal view and the (**B**) left anterior oblique caudal projection. LAD, left anterior descending; LCx, left circumflex; OM, obtuse marginal.

node 60 percent of the time, a minority of patients depend on an atrial branch of the LCx.[9] In approximately 90 percent of patients, the AV node receives blood supply from the AV nodal branch off of the distal RCA.[1]

The PDA courses along the posterior interventricular groove to supply the posterior and inferior free walls of the LV. The PDA gives off several small septal branches which supply the inferior portion of the interventricular septum, the posteromedial mitral papillary muscle, as well as the right and a portion of the left bundle branch.[7,8] The posteromedial muscle of the mitral valve is supplied by the PDA while the LAD and LCx provide dual supplies to the anterolateral

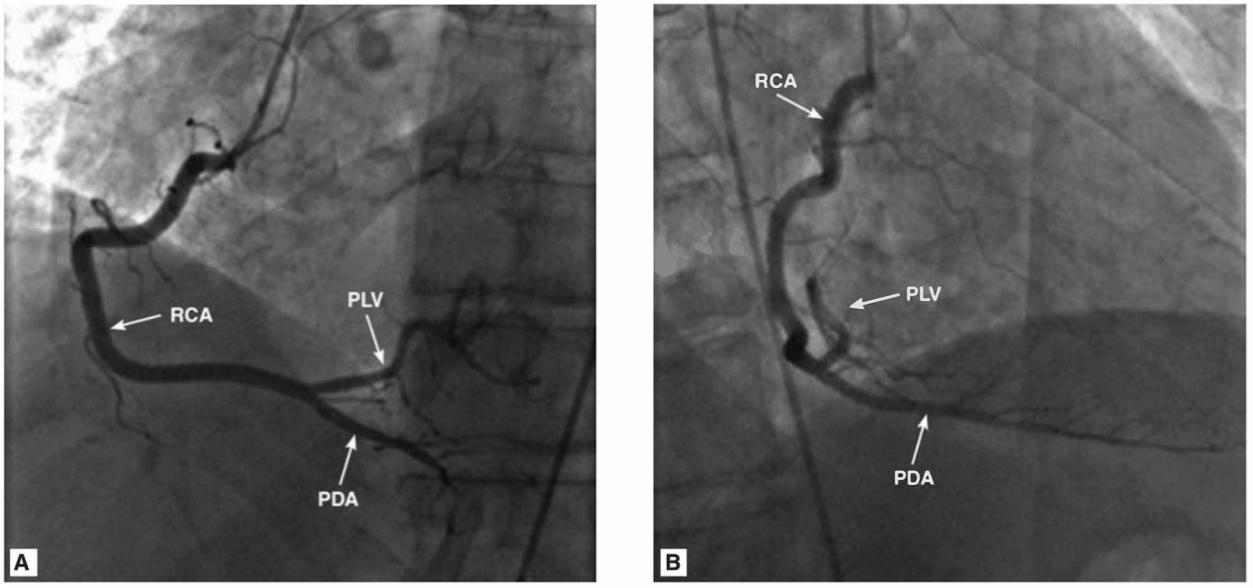



**FIGURE 55-4** **A.** The right coronary artery (RCA) in the left anterior oblique cranial projection. **B.** The RCA in the right anterior oblique view. PDA, posterior descending artery; PLV, posterior lateral ventricular branch.

mitral papillary muscle. As a result, an inferior wall MI involving the RCA or a dominant LCx is the most common cause of acute ischemic mitral regurgitation.

Coronary angiography was performed in 126,595 patients, and an anomalous coronary artery was present in 1.3 percent.[10] The most common coronary anomaly is the LAD and LCx arising from separate ostia (30.4 percent), and the second most common anomaly is the LCx originating from the right sinus or the proximal RCA (27.7 percent).[10] Although 81 percent of coronary anomalies are benign, there are several potentially serious anomalies such as the LM arising from the pulmonary artery (Bland–White–Garland Syndrome) and the LM originating from the right aortic sinus and taking an interarterial course (between the pulmonary artery and aorta).[1] This variant is considered benign if the LM arises from the right sinus and takes a septal, anterior, or retroaortic course. Coronary fistulas account for 10 percent of all coronary anomalies, and while small fistulas are relatively benign, patients with a large coronary fistula may present with angina or heart failure.[9] Patients with congenital heart disease, such as a bicuspid aortic valve or tetralogy of Fallot, frequently have an anomalous coronary artery.[1]

Coronary arteries communicate via anastomotic channels, and in patients with normal or minimal CAD, these collaterals are not usually seen due to their small size (50–200 μm in diameter).[7,11] However, collaterals gradually develop and enlarge when there is severe obstructive CAD secondary to a pressure gradient generated across the channel.[7,11] Collaterals provide approximately 50 percent of coronary flow in occluded vessels and are sufficient to protect the myocardium from infarction and ischemia at rest.[11] However, during provocative testing such as exercise stress testing, a collateral-dependent territory will generally show evidence of inducible ischemia.

## CORONARY ANGIOGRAPHY

When performing coronary angiography, at least two orthogonal views are needed for each vessel to properly assess the severity of eccentric lesions, and at least five views are recommended to adequately evaluate the left coronary system. Traditionally, images were acquired at 30 frames/s, but most labs today obtain images at 15 frames/s. Thirty frames/s is recommended if the patient is tachycardic or has a high-flow state.[1] Image quality in some projections, such as LAO cranial, is improved by acquiring images when the patient takes a deep breath, and vessel overlap is decreased by using angulated views.[1] Contrast injection by hand should start slowly with a gradual augmentation in force to prevent catheter disengagement, and the injection must be strong enough to cause a reflux of contrast into the sinus of Valsalva, enabling adequate visualization of the ostium.[1] Contrast injections should be sufficient to fully opacify the vessel lumen. Hand controlled automated injectors are becoming more popular in catheterization laboratories and facilitate adequate opacification of the coronary arteries especially when using 4F or 5F catheters. Extreme caution is required to avoid injecting air into the coronary circulation.

The LM is usually approached in the 30° LAO projection with a JL 4 catheter. Slight counterclockwise rotation might be warranted to move the catheter in an anterior direction to properly engage the LM. Conversely, clockwise rotation may be required to move the catheter in a posterior direction if it is not coaxial with the LM.[1] Clockwise rotation of a JL 5 or even JL 6 catheter may be required to engage the LM in the setting of a dilated aorta.[1] Forceful injection of contrast into the LM might result in dissection if there is damping or if the catheter is oriented upward against the roof of the LM and not coaxial with the LM.[1] Although the JL 4 normally engages the LM without manipulation, an Amplatz catheter might be necessary if the LM is anomalous or has an unusual orientation. Amplatz catheters are associated with a higher risk of catheter induced coronary dissection.[1]

Severe LM disease is extremely dangerous and suggested by damping or ventricularization of the pressure wave form upon catheter engagement. The best views to visualize the ostial LM are either the shallow LAO or the LAO cranial projections. A distal LM stenosis is best seen in an AP caudal or shallow RAO caudal view. RAO caudal and LAO cranial projections should be used to view the proximal LAD, and the AP, LAO, and RAO cranial views are recommended to visualize the mid and distal LAD as well as the diagonal branches (Fig. 55-2). Although the lateral view increases radiation exposure to the operator, it is helpful in evaluating mid LAD lesions. The LCx and obtuse marginal branches are best seen in the AP caudal and shallow RAO and LAO caudal projections (Fig. 55-3). The LAO caudal view is recommended for visualizing the origin of the ramus intermedius and the LAO cranial projection is the best for evaluating a left PDA.

The RCA is engaged in the 30° LAO projection with a JR 4 catheter. After advancing the JR 4 catheter to the aortic valve, the catheter is pulled back approximately 2 to 3 cm and turned clockwise in an anterior direction. The proximal and mid-RCA are best visualized in the LAO view (Fig. 55-4A). The 30° cranial AP projection is used for evaluating the distal RCA bifurcation and the origin of the RPDA and RPLV branches, and the midsegment of the RPDA is best seen using a shallow RAO view (Fig. 55-4B). The right lateral projection can help visualize the ostial and mid segments of the RCA and the origin of the acute marginal branches.

Coronary artery bypass grafts should be visualized in the same projections recommended for visualization of the native target vessels. The distal anastomosis of the bypass graft and the coronary artery is a frequent site of disease and must be evaluated carefully. Bypass grafts to the RCA should be engaged in the LAO projection and are usually more anterior and more caudal than grafts to the left coronaries. Left coronary bypass grafts should be engaged in the RAO view. Frequently, the sequence of the ostia of venous grafts in a cranial to a caudal direction is the second obtuse marginal branch, first obtuse marginal, ramus intermedius, diagonal, and then the LAD.[1] Most saphenous vein grafts can be

engaged with a JR 4 catheter and, if the graft is occluded, an injection is performed to verify the stump. An aortogram in the 30° LAO projection using approximately 40 to 50 mL of contrast might be necessary to locate grafts.[1]

Caution should be taken when engaging the RIMA and LIMA grafts due to the risk of dissection. The brachiocephalic or left subclavian artery should be cannulated by a JR 4 catheter, and then an exchange length J-tipped guide wire should be passed carefully into the respective distal subclavian artery. Catheters should not be advanced into the right or left subclavian artery unless over a guide wire. After the JR 4 catheter is removed, the IMA catheter is advanced slowly over the exchange guide wire. The IMA catheter is then slowly pulled back and torqued in the appropriate direction to engage the RIMA and LIMA grafts. The LIMA is generally engaged by pulling the IMA catheter back and by turning it counterclockwise or in an anterior direction. The catheter should be maintained in a coaxial orientation with the IMA during contrast injection to avoid causing a catheter-induced dissection.

## ISCHEMIC HEART DISEASE

The magnitude of the impact of CAD is extensive. Ischemic heart disease is the number one cause of death both in the United States and worldwide, and its incidence and prevalence continue to increase secondary to an aging population and an increase in obesity and diabetes.[12] Approximately 13 million Americans are affected by CAD, and slightly more than 50 percent of these patients have suffered from a MI.[12] The economic burden of CAD exceeded US$142.5 billion in the United States in 2006. After the age of 40, the lifetime risk for developing ischemic heart disease is 53 percent for men and 32 percent for women.[12]

The most common etiology of MI is plaque rupture and subsequent thrombus formation, but angina usually results from supply and demand mismatch. Supply is a function of coronary flow and arterial oxygen saturation, and demand is affected by heart rate, contractility, and LV wall stress. Classically, angina presents as substernal or left-sided crushing or squeezing chest pressure with radiation to the left arm and is frequently associated with dyspnea, diaphoresis, nausea, and vomiting. Angina is usually precipitated by exertion and relieved by rest and nitroglycerin. Ischemia can also manifest as dyspnea on exertion secondary to elevated left-sided filling pressures.

The initial evaluation of patients with chest pain includes a thorough history and physical exam, serum markers of myocardial necrosis, and a resting ECG. The resting ECG is normal in approximately 50 percent of patients with angina. Although cardiac enzymes such as troponin and creatine kinase rise within 3 h of myocardial injury and provide significant prognostic information, these biomarkers are usually normal in patients with angina.[12] Although a patient with ischemic ECG changes and/or elevated cardiac enzymes should be referred for cardiac catheterization, noninvasive stress testing is recommended in patients with an intermediate pretest probability of having CAD.[12] Exercise electrocardiography has a sensitivity and specificity of 68 and 77 percent, respectively.[12] The test is limited by the patient's ability to achieve their target heart rate and the requirement of a normal ECG at baseline. In patients who are unable to exercise and in those with abnormal resting ECGs, myocardial imaging is recommended, which markedly increases the prognostic power of the test. Myocardial perfusion imaging using adenosine has a sensitivity of 90 percent and a specificity of 82 percent.[12] Adenosine is very safe but contraindicated in patients with severe bronchospasm, high-grade heart block, and in those taking dipyridamole. Stress echocardiography using dobutamine has a sensitivity of 81 percent and a specificity of 79 percent, but its use is limited in patients with poor echocardiographic windows, ventricular arrhythmias, and left bundle branch block.[12]

Although noninvasive testing plays an integral role in diagnosing CAD, coronary angiography remains the gold standard. By coronary angiography, a lesion is considered to be severe if there is greater than a 70 percent narrowing of the luminal diameter, and a mild stenosis is defined as less than a 30 percent blockage. Results of coronary angiography in patients with stable angina are single-vessel disease in 25 percent, double-vessel disease in 25 percent, triple-vessel disease in 25 percent, significant LM disease (>50 percent stenosis) in 10 percent and 15 percent have nonobstructive CAD.[12] For intermediate lesions of uncertain significance, other techniques such intravascular ultrasound (IVUS) and fractional flow reserve (FFR) can be used to assess disease severity and to guide therapy. IVUS delineates and quantifies the atherosclerotic burden and consistently demonstrates that lesions are underestimated using angiography alone.[12] Although minimal luminal area and area stenosis as measured by IVUS provide additional information to angiography, FFR is probably the better test for determining both physiological ischemia (disease severity) and the need for revascularization.[13,14] However, IVUS might be preferable for evaluating LM disease and transplant vasculopathy.[15] FFR is performed by crossing the lesion of interest with a 0.014-in pressure wire and, after the administration of adenosine, the pressures distal and proximal to the stenosis are obtained. A ratio of distal pressure to proximal pressure of less than 0.75 to 0.80 is deemed abnormal. The sensitivity of FFR for detecting reversible ischemia is 88 percent, and the specificity is 100 percent.[14]

As compared to medical therapy, CABG has been shown to improve survival in patients with LM disease (>50 percent stenosis), triple-vessel CAD especially with LV dysfunction, and double-vessel CAD including severe proximal LAD disease. However, the survival benefit of CABG decreases over time due to eventual graft failure and emergence of new disease in ungrafted vessels. Although revascularization of single-vessel disease does not improve survival over optimal medical management, it does alleviate symptoms and improve quality of life.

CABG is preferred over percutaneous coronary intervention (PCI) in patients with unprotected LM involvement,

triple-vessel disease, diabetics with multivessel disease, and double-vessel CAD when it includes the proximal LAD. CABG is also preferable in patients requiring surgery for valvular disease.

## PERCUTANEOUS CORONARY INTERVENTIONS

Over the past 30 years, PCI has become the first line treatment of CAD, with approximately 500,000 interventions performed each year in the United States.[16] The first percutaneous transluminal coronary angioplasty (PTCA) was performed by Andreas Gruentzig in 1977. Since that time, numerous devices have emerged such as stents, atherectomy catheters, cutting balloons, thrombectomy catheters, radiation therapy, and lasers. As a result of decades of technical advances, the success of PCI is as high as 95 percent while the risk of death and emergent CABG is considerably less than 1 percent.[16]

PCI is generally performed through 6F guiding catheters but some specialized procedures such as large burr rotational atherectomy and bifurcational stenting require 7F or 8F catheters. The LM or RCA ostium is engaged with a guide catheter and, following the administration of adequate anticoagulation, the stenosis is crossed with a 0.014-in guide wire. A coronary angioplasty balloon is then advanced over the guide wire and after confirming proper placement with fluoroscopy, the balloon is inflated at the site of stenosis. Balloon angioplasty increases luminal diameter primarily by creating a dissection in the atherosclerotic plaque. In the process of enlarging the lumen, angioplasty also denudes endothelium and disrupts, cracks, and fissures atherosclerotic plaque resulting in accumulation of platelets and fibrin.[16] Balloon angioplasty is associated with a 5 percent risk of abrupt closure and a 50 percent risk of angiographic restenosis (>50 percent in-stent stenosis) within 6 months.[16] Nevertheless, balloon angioplasty was shown to improve outcomes compared to thrombolytic therapy in the setting of acute MI, and it was shown to alleviate angina better than optimal medical therapy alone.[16]

Bare metal intracoronary stents were first approved by the FDA in 1993 to treat acute or threatened closure and in 1994 to reduce restenosis compared to balloon angioplasty alone. The implantation of bare metal stents (BMS) became commonplace and markedly reduced complications such as abrupt closure and need for emergent bypass surgery. BMS decrease restenosis by nearly 50 percent compared to balloon angioplasty and, in general, there is a 20 to 30 percent risk of in-stent angiographic restenosis at 6 months following implantation of a BMS. BMS implantation requires aspirin indefinitely and clopidogrel for at least 1 month.

The first drug-eluting stent (DES) was approved by the FDA in 2003, and newer generation DES have been shown to reduce the risk of restenosis to as low as 5 percent at 12 months. DES implantation has been shown to be superior to BMS implantation in a wide range of patients including those with acute MI, acute coronary syndromes, stable CAD, diabetes, and renal insufficiency.[17–19] In the setting of acute MI, target lesion revascularization was decreased by one-third in patients receiving a DES[17] compared to BMS. In patients with either diabetes and/or chronic renal insufficiency, DES as compared to BMS had a lower incidence of major adverse cardiac events (death, nonfatal MI, or target vessel revascularization).[18,19] DES are also associated with better clinical outcomes than BMS in the treatment of unprotected LM disease and saphenous vein graft lesions.[20,21]

The enthusiasm and use of DES were drastically affected several years ago following preliminary reports suggesting an increased risk of late and very late stent thrombosis. This potentially catastrophic event is associated with major cardiac events including MI and death. After DES implantation, patients must take chronic aspirin and clopidogrel for at least 12 months to mitigate the risk of stent thrombosis. According to a recent study, the continuation of clopidogrel after 12 months failed to reduce the incidence of late stent thrombosis associated with DES.[22] However, a meta-analysis of 10 randomized studies that included 5030 patients demonstrated that stent thrombosis occurred at a similar rate after both DES (0.58 percent) and BMS (0.54 percent).[23] In fact, the incidence of stent thrombosis was indistinguishable (1.4 percent) after BMS and DES implantation in 3405 patient presenting with acute coronary syndromes (Fig. 55-5).[24]

Over the past 2 decades, the emergence of stents and the use of antiplatelet therapy have markedly decreased the incidence of severe periprocedural ischemic complications of PCI. Composite rates of Q wave MI, emergent CABG, and death are less than 1.0 percent. Higher volume centers (>400 cases annually) have lower complication rates than low-volume centers and high-volume operators (>75 cases annually) have lower complication rates than low-volume operators.[25] Other complications of PCI include distal embolization, coronary artery dissection, intramural hematoma, occlusion of side branches, and coronary artery perforation, which occur in 0.84 percent of cases.[26] Access site complications such as hematomas (major and minor), pseudoaneurysm formation, retroperitoneal bleeding, need for blood transfusion, arteriovenous fistula, and arterial occlusion are significant causes of morbidity associated with PCI and occur more frequently after PCI than diagnostic procedures, with an incidence as high as 6 percent.[27] Severe bleeding, minor bleeding, and surgical repair of the vascular access site occurs in 3, 10, and 1.4 percent of patients undergoing PCI from the femoral site and are related to the use of dual antiplatelet therapy and procedural anticoagulation.[27]

Other devices are also commonly used to increase immediate procedural success of PCI. The effect of these devices on long-term outcomes is less clear. Rotational atherectomy is performed to debulk heavily calcified lesions prior to stent deployment.[16] Cutting balloons have been shown to be superior to PTCA in the treatment of in-stent restenosis, and they may have an advantage during bifurcational interventions.[16] In the setting of acute MI, manual aspiration using a thombectomy catheter increases myocardial reperfusion and reduces myocardial necrosis.[8,28] Manual aspiration thrombectomy is

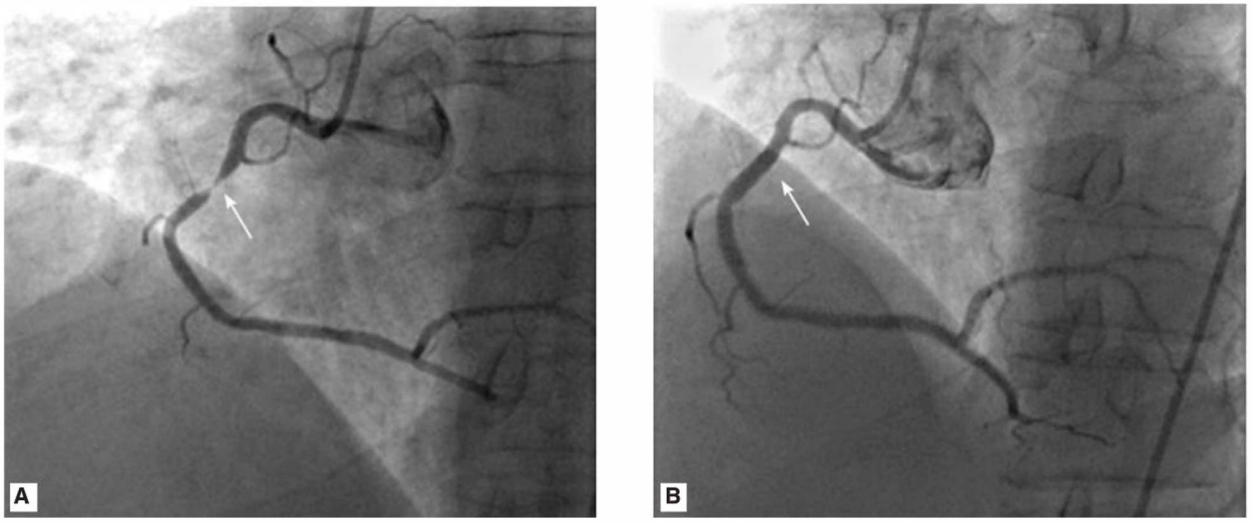



**FIGURE 55-5** **A.** This patient presented with an acute coronary syndrome and had a severe mid-RCA stenosis. **B.** Following placement of a drug-eluting stent, the patient had resolution of his chest pain and ST-segments.

also associated with a decreased risk of no reflow and distal embolization as compared to PTCA or stenting alone.[8,28]

PCI is indicated for the treatment of in-stent restenosis and severe single- or double-vessel CAD with demonstrable ischemia on stress testing. PCI is preferable over CABG in nondiabetic patients with preserved LV function, patients with a patent LIMA to the LAD, patients with multiple debilitating comorbidities who are high risk for CABG, elderly frail patients, patients with short life expectancies, and in those who need urgent noncardiac surgeries.

## INVASIVE HEMODYNAMICS

An essential part of cardiac catheterization is the acquisition and interpretation of hemodynamics. Cardiac output is a critical variable used to assess the systolic performance of the LV, and it is frequently obtained during right heart catheterization by the Fick and/or thermodilution method. Doppler flow velocity is also capable of measuring cardiac output, but this echocardiographic technique is more vulnerable to human error than invasive testing.[29] The most accurate measure of cardiac output at high-output states is thermodilution, while the Fick method is more accurate in patients with low-output conditions and atrial fibrillation.[29] The error in calculating cardiac output invasively is approximately 15 percent, and it might be slightly less for the Fick method.[29]

The Fick formula for cardiac output is:

$$\textit{Cardiac output} = O_2\ \textit{consumption}/(A\text{–}V)O_2 \times \textit{hemoglobin concentration} \times 1.36 \times 10$$

$O_2$ consumption is measured via a gas exchange face mask, but it can also be estimated using a patient's body weight. $(A\text{–}V)O_2$ is the arterial–venous oxygen difference.

Thermodilution cardiac output involves injection of a cold saline bolus into the right atrium, and changes in temperature are measured in the pulmonary artery after the cold saline mixes with the warm blood distally.[29] Cardiac output is dependent on a temperature or time intensity curve, where time is on the *x*-axis, and concentration is on the *y*-axis. Cardiac output is inversely related to the area under the curve. This method is inaccurate in patients with irregular heart rhythms, tricuspid regurgitation, and pulmonic regurgitation. In the absence of a cardiac output measurement, pulmonary artery saturation can be used to estimate LV function, and a saturation less than 65 percent is suggestive of low output.[29]

Cardiac catheterization is the only method capable of directly measuring pressures in the heart and great vessels. Pressure waveforms are passed from the cardiac chambers or great vessels to a pressure transducer via a fluid-filled catheter. The transducer produces an electrical potential that is proportional to variations in pressure, and these electrical potentials are displayed as intracardiac pressure tracings. Normal pressure of the right atrium and RV is 5 and 25/5 mm Hg, respectively. Pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), and LV pressures are normally 25/10, 10, and 120/10 mm Hg,[29] respectively.

Cardiac catheterization is also used to assess for intracardiac shunting. During a right-heart catheterization, a shunt should be suspected when there is a "step-up" on measurements of right-heart oxygen saturations, and the degree of shunting is reported as the $Q_p/Q_s$. $Q_p/Q_s$ is calculated using the following formula:

$$Q_p/Q_s = \textit{arterial } O_2 \textit{ sat} - \textit{mixed venous sat}/\textit{pulmonary vein sat} - \textit{pulmonary arterial sat}$$

$$\textit{Mixed venous sat} = 3\ \textit{SVC} + 1\ \textit{IVC}/4$$

Patients with valvular heart disease are frequently referred for left- and right catheterization. The severity of mitral stenosis is assessed by obtaining a gradient between the LV and the left atrium, which requires a transseptal puncture. As a result, it is simpler and faster to use the PCWP as an estimate of left atrial pressure.

Aortic valve gradients are used to determine the severity of aortic stenosis and can be obtained by a variety of methods. A peak-to-peak gradient is calculated by subtracting the peak aortic pressure from the peak LV pressure. An aortic valve gradient can also be obtained by the "pull-back method" in which a catheter is quickly pulled back from the LV and placed in the aorta. However, the best method for obtaining an aortic gradient is to perform simultaneous pressure measurements in the LV and aorta using a double-lumen catheter. The modified Hakki equation can be used to measure aortic valve area:

*Aortic valve area = cardiac output/square root of the peak-to-peak pressure gradient*

## VALVULAR HEART DISEASE

The most common valvular abnormalities encountered in clinical practice are aortic stenosis, aortic regurgitation, mitral stenosis, and mitral regurgitation. Aortic stenosis remains the most common acquired valvular abnormality and is frequently caused by progressive calcification of a trileaflet or congenitally bicuspid valve. Calcification extends from the base of the cusps to the leaflets, restricting leaflet motion and decreasing valve area without fusion of the commissures.[30] In contrast, rheumatic disease is characterized by commissural fusion and scarring, and is almost always accompanied by mitral valve disease.[30]

Aortic stenosis causes LV systolic pressure overload. The LV gradually adapts through a hypertrophic process characterized by an increase in wall thickness and maintenance of LV volume.[30] If increase in wall stress is out of proportion to the compensatory increase in concentric hypertrophy, the ejection fraction (EF) is reduced secondary to high afterload. Depressed contractility may also contribute to a low EF and, frequently, the etiology of the compromise in LV systolic function is unclear. Regardless, the distinction has important clinical implications as surgery is less advantageous when the reduction in EF is due to depressed contractility as opposed to an increase in afterload.[30] Although the progression of concentric hypertrophy is protective against high LV pressure, it limits coronary vasodilator reserve and reduces coronary flow per gram of muscle, resulting in subendocardial ischemia.[30]

Initially, there is a long latent period associated with minimal morbidity and mortality, but once aortic stenosis is considered to be moderate in severity (aortic valve area of 1.0–1.5 $cm^2$, mean gradient of 25–40 mm Hg, or jet velocity greater than 3.0 m/s), valve area decreases approximately 0.1 $cm^2$/year, jet velocity increases 0.3 m/s/year, and mean pressure gradient increases 7 mm Hg/year.[30] Sudden death is extremely rare (<1 percent) in asymptomatic patients with aortic stenosis, but after the onset of symptoms, which include angina, heart failure, and syncope, there is a marked increase in sudden cardiac death with an average survival without treatment of 2 to 3 years.[30] As a result, the management of patients with aortic stenosis is dictated by the presence of symptoms.

Cardiac catheterization serves an integral role in the evaluation and treatment of aortic stenosis and is indicated in patients at risk for CAD prior to surgery. If there is a discrepancy between clinical and echocardiographic findings or if the noninvasive tests are inconclusive, a hemodynamic evaluation is recommended to obtain both an aortic gradient and an aortic valve area.

Aortic valve replacement is indicated for symptomatic aortic stenosis and for severe aortic stenosis in patients with depressed LV function (EF less than 50 percent) or coexisting CAD requiring CABG. Valve replacement is also reasonable in asymptomatic patients with an abnormal response to exercise testing or if there is a critical stenosis (valve area less than 0.6 $cm^2$, mean gradient greater than 60 mm Hg, and jet velocity greater than 4.0 m/s) and the operative mortality is less than 1 percent.[30]

Prior to the first balloon aortic valvuloplasty (BAV) in 1985, observation was the only option for inoperable patients.[31] BAV has been shown to improve symptoms, LV function, and hemodynamics, and it enables much sicker and older patients to eventually undergo surgery.[31] BAV fractures valve leaflet calcification, stretches the annulus, and separates the commissures. This increases aortic valve area, reduces transvalvular pressure gradients, and mildly augments LV systolic function.[32] However, there is a limited role for percutaneous BAV secondary to short-term benefits, high rates of restenosis, and at least a 10 percent risk of severe complications.[31,32] The incidence of death, stroke, and vascular complications following BAV is 5, 2, and nearly 6 percent, respectively.[31,32] Other complications include LV perforation, MI, arrhythmias, and aortic regurgitation.[31,32]

BAV rarely increases aortic valve area greater than 1.0 $cm^2$ and, although it improves symptoms, clinical deterioration frequently occurs within 6 to 12 months.[32] BAV was performed in 144 patients who were not offered valve replacement secondary to high surgical risk.[32,33] Group 1 (57 percent) required no further treatment, group 2 (19 percent) needed a second valvuloplasty due to restenosis, and group 3 (24 percent) eventually underwent valve replacement.[32,33] At 36-month follow-up, survival was 13 and 20 percent for groups 1 and 2, respectively, and it was 75 percent for group 3.[32,33] In unstable patients who are too high risk for aortic valve replacement, BAV is a reasonable option as a bridge to surgery.[32,33] It is also appropriate to perform palliative BAV in an inoperable patient with severe symptomatic aortic stenosis and poor quality of life.[30,32]

Given the limitations of BAV, transcatheter aortic valve replacement (TAVR) of balloon expandable or self-expanding aortic valves has emerged as a viable option in both high risk and extreme risk, inoperable patients. The PARTNER Trial (Cohort B) compared the transcatheter Edwards Sapien aortic

valve to medical therapy in aortic stenosis patients deemed as extreme-risk or inoperable.[34–36] There was a marked decrease in all-cause mortality and cardiovascular mortality in the TAVR treated patients compared to the medically treated patients at 1 and 2 years of follow-up. Based on these results, the Edwards Sapien valve was approved by the FDA in November, 2011 for use in extreme risk or inoperable aortic valve patients. The PARTNER Trial (Cohort A) compared TAVR to surgical aortic valve replacement (SAVR) in high-risk patients. The all-cause mortality between TAVR and SAVR was comparable at 1 and 2 years, although the stroke rate was higher in the TAVR treated group.[37,38] Based on these data, the Edwards Sapien valve was also approved by the FDA for high risk (STS score >10%) patients. Similar clinical trials with the self-expanding Medtronic CoreValve are currently underway in the United States. It should be noted that the catheter systems for TAVR have been approved in many countries for several years and over 100,000 patients have been treated worldwide with TAVR. TAVR results in clinical and hemodynamic improvement and is associated with high procedural success, even in critically ill patients.[34] An aortic valve prosthesis can be successfully implanted percutaneously in 96.9 percent of patients.[39] The balloon expandable Edward SAPIEN valve can be delivered via a transfemoral or transapical approach. The self-expanding Medtronic CoreValve can be delivered via a transfemoral, subclavian or direct aortic approach. Major adverse cardiovascular complications occur in up to 10 percent of patients at 30 days and mortality, mostly secondary to severe comorbid conditions of these high-risk patients, is approximately 20 to 30 percent at 1 year.[34] Further studies of TAVR are warranted in intermediate risk patients and are in progress. As further technological improvements are made in percutaneous aortic valve delivery systems, this therapy will likely continue to expand to a greater subset of patients.

Common etiologies of aortic insufficiency include myxomatous degeneration, congenital abnormalities such as a bicuspid aortic valve, calcific degeneration, rheumatic heart disease, infectious endocarditis, hypertension, idiopathic dilatation of the aorta, ascending aortic dissection, and Marfan syndrome. Syphilis, rheumatoid arthritis, osteogenesis imperfecta, Ehlers–Danlos syndrome, Reiter syndrome, and anorectic drugs can rarely be the cause. Chronic aortic regurgitation results in volume overload and LV dilatation due to increased afterload. It progresses slowly over a long period of time in the absence of symptoms. In contrast, patients with acute regurgitation from endocarditis, dissection, or trauma present with cardiogenic shock or pulmonary edema secondary to abrupt elevation of left-sided filling pressures and a sudden drop in cardiac output. Acute aortic insufficiency can also lead to ischemia and sudden death.

Early in the disease process, LV dysfunction and dilation can be improved with aortic valve replacement. Left untreated, the LV eventually dilates further and adopts a more spherical geometry. At this point, LV systolic dysfunction is a product of reduced contractility and is irreversible with minimal if any survival benefit from surgery. This is why LV systolic function and LV end-systolic diameter are the most significant determinants of postoperative systolic function and survival.[30]

The rate of sudden death in asymptomatic aortic regurgitation is less than 0.2 percent per year, and asymptomatic patients with aortic insufficiency develop symptoms or LV dysfunction at a rate of 4.3 percent per year.[30] Asymptomatic patients with aortic insufficiency and depressed LV systolic function develop symptoms within 2 to 3 years, and rates of sudden death in patients with heart failure are as high as 20 percent per year.[30]

Aortic valve replacement is indicated in symptomatic patients with severe aortic regurgitation regardless of LV function. It is also recommended in asymptomatic patients with severe aortic regurgitation and depressed LV function (EF less than 50 percent) and in patients with severe aortic regurgitation who are undergoing CABG. Aortic valve replacement is reasonable in asymptomatic patients with severe regurgitation and normal LV function if there is severe LV dilatation (LV end-diastolic dimension greater than 75 mm or end-systolic dimension greater than 55 mm). Aortic valve replacement and aortic root reconstruction are recommended if there is aortic insufficiency and the aortic root exceeds 4.5 to 5.0 cm. Coronary angiography should be performed prior to surgery in patients at high-risk for CAD. Patients with discrepant clinical and echocardiographic findings should be referred for cardiac catheterization with an aortic root angiogram.

The most common etiology of mitral stenosis is rheumatic heart disease. Rheumatic mitral valve disease is characterized by leaflet thickening and calcification, commissural fusion, and chordal fusion. Isolated involvement of the mitral valve occurs in 40 percent of patients with rheumatic heart disease and is more common in women.[30] Mitral stenosis prevents adequate opening of the mitral valve during diastole, obstructing flow from the left atrium into the LV. A pressure gradient between the left atrium and LV is generated to open the mitral valve and drive blood into the LV. Chronic elevation of left atrial and pulmonary venous pressure causes pulmonary arteriolar vasoconstriction, intimal hyperplasia, and medial hypertrophy, eventually resulting in pulmonary arterial hypertension.

The mitral valve orifice is normally between 4.0 and 5.0 $cm^2$, and symptoms at rest may develop if the mitral valve area is less than 1.5 $cm^2$.[30] Symptoms may also occur with an area less than 2.5 $cm^2$ if there is an increase in left atrial pressure from either an augmentation in mitral flow or a reduction in diastolic filling secondary to atrial fibrillation, pregnancy, exercise, or stress.[30] Although mitral stenosis is initially a slow, stable, progressive disease with a latent period of 20 to 40 years from the time of rheumatic fever to the onset of symptoms, its course accelerates, and symptoms become disabling within a decade. Most patients in the United States present with mitral stenosis in their 50s to 60s, and greater than one-third of patients referred for valvotomy are older than 65. Ten-year survival of untreated patients presenting with mitral stenosis ranges from 50 to 60 percent, but depends on the severity of symptoms.

Survival is greater than 80 percent at 10 years in asymptomatic or mildly symptomatic patients, but the average survival is only 3 years in patients presenting with severe pulmonary hypertension.[30]

Doppler echocardiography is the preferred diagnostic tool for evaluating mitral stenosis, but cardiac catheterization is indicated when the echocardiogram is inconclusive or if there is discrepancy between clinical findings and noninvasive tests. Catheterization is also recommended if there is a discrepancy between the Doppler-derived valve area and mean gradient. It is reasonable to perform cardiac catheterization to assess hemodynamic response to exercise and to determine the etiology of severe pulmonary arterial hypertension when it is disproportionate to the magnitude of mitral stenosis as measured by noninvasive testing.[30]

Percutaneous mitral balloon valvotomy was introduced in the early 1980s and the Inoue valvuloplasty balloon was approved by FDA in 1994. Mitral valvuloplasty is preferred over surgery in appropriately selected patients who have noncalcified, pliable valves and minimal fusion of the subvalvular apparatus. Percutaneous mitral balloon valvuloplasty involves transseptal puncture and sequential inflation of the hourglass-shaped Inoue balloon across the mitral valve in an effort to open the fused commissures. Mitral valvuloplasty is successful in 80 to 95 percent of patients, and it has been shown to double the valve area, decrease the transmitral pressure gradient by 50 to 60 percent, and alleviate symptoms.[30]

Percutaneous mitral balloon valvotomy is recommended for symptomatic patients with moderate or severe mitral stenosis (valve area less than 1.0 $cm^2$, mean gradient greater than 10 mm Hg, or pulmonary artery systolic pressure greater than 50 mm Hg) and favorable valve morphology for percutaneous valvuloplasty in the absence of moderate-to-severe mitral regurgitation and left atrial thrombus.[30] It is indicated for asymptomatic patients with moderate or severe mitral stenosis and favorable valve morphology who have pulmonary hypertension (pulmonary artery systolic pressure greater than 50 mm Hg at rest and 60 mm Hg with exercise). Percutaneous mitral balloon valvulopasty is reasonable for asymptomatic patients with moderate or severe mitral stenosis if they have new onset atrial fibrillation. Percutaneous mitral balloon valvotomy should not be performed in patients with either mild mitral stenosis, left atrial thrombus, moderate-to-severe mitral regurgitation, or heavily calcified valve leaflets.[30]

Percutaneous mitral balloon valvuloplasty is associated with a mortality rate of less than 1 to 2 percent.[30] The most common complication is severe mitral regurgitation, and it occurs in 2 to 4 percent of cases.[30] Other complications include atrial septal defects (ASDs), embolization, LV perforation, and bleeding complications. At 3 to 7 years, freedom from repeat valvotomy, mitral valve surgery, or death is as high as 80 to 90 percent in patients with favorable mitral valve morphology.[30] Valvular calcification, thickened leaflets with impaired mobility, and subvalvular fusion increase risks for complications and rates of recurrent stenosis.[30] Randomized controlled trials comparing percutaneous balloon valvotomy with both open and closed surgical commissurotomy revealed comparable improvements in hemodynamics, exercise capacity, symptoms, and event-free survival.[30]

## HEART FAILURE

Heart failure is a growing epidemic due to an aging population, decreased mortality following MI, and improvements in therapies for CAD and cardiomyopathy. Five million Americans suffer from heart failure, and nearly 550,000 patients are diagnosed with new onset heart failure each year.[40] Approximately 80 percent of patients hospitalized with heart failure are more than 65 years of age, and after the age of 65, 10 per 1000 of the population are affected by this condition.[40] Annually, heart failure accounts for at least 1 million hospitalizations, 6.5 million hospital days, 15 million office visits, and approximately US$27.9 billion in direct and indirect costs.[40] Despite improvements in heart failure treatment, the number of deaths attributed to heart failure continues to rise.

Heart failure is not synonymous with LV dysfunction or cardiomyopathy; rather, it is a clinical syndrome associated with characteristic symptoms of shortness of breath and fatigue and various physical examination findings such as a third heart sound, jugular venous distension, crackles, and peripheral edema.[40] Heart failure is caused by either a structural or functional process that impairs diastolic or systolic LV function. This results in diminished exercise tolerance secondary to low cardiac output and pulmonary congestion with retention of fluid causing peripheral edema.[40] Using the old term "congestive heart failure" is now discouraged because not all patients presenting with heart failure have evidence of volume overload.[40]

Most common causes of heart failure are ischemic heart disease, hypertension, and dilated cardiomyopathy. Etiologies of dilated cardiomyopathy include idiopathic, genetic (30 percent), infectious (HIV), infiltrative diseases (hemachromatosis, sarcoid, amyloid), toxins (cocaine, alcohol, adriamycin), peripartum, nutritional deficiencies (thiamine), tachycardia, and endocrine disorders (hyperthyroidism and pheochromocytoma). Approximately, 50 percent of patients who present with symptoms and signs of heart failure have a normal or preserved LV EF, which is called diastolic dysfunction or heart failure with preserved LV systolic function. The incidence of diastolic dysfunction increases with age. Although the overall incidence of diastolic dysfunction is around 35 percent, nearly 50 percent of patients over the age of 70 are affected by this condition. Heart failure can also be caused by hypertrophic cardiomyopathy and restrictive cardiomyopathy.

Heart failure is a clinical diagnosis, and it cannot be confirmed by one diagnostic test. A thorough history and physical exam are essential to diagnosing and identifying the etiology of heart failure. A transthoracic echocardiogram evaluates LV function, valves, pericardium, pulmonary

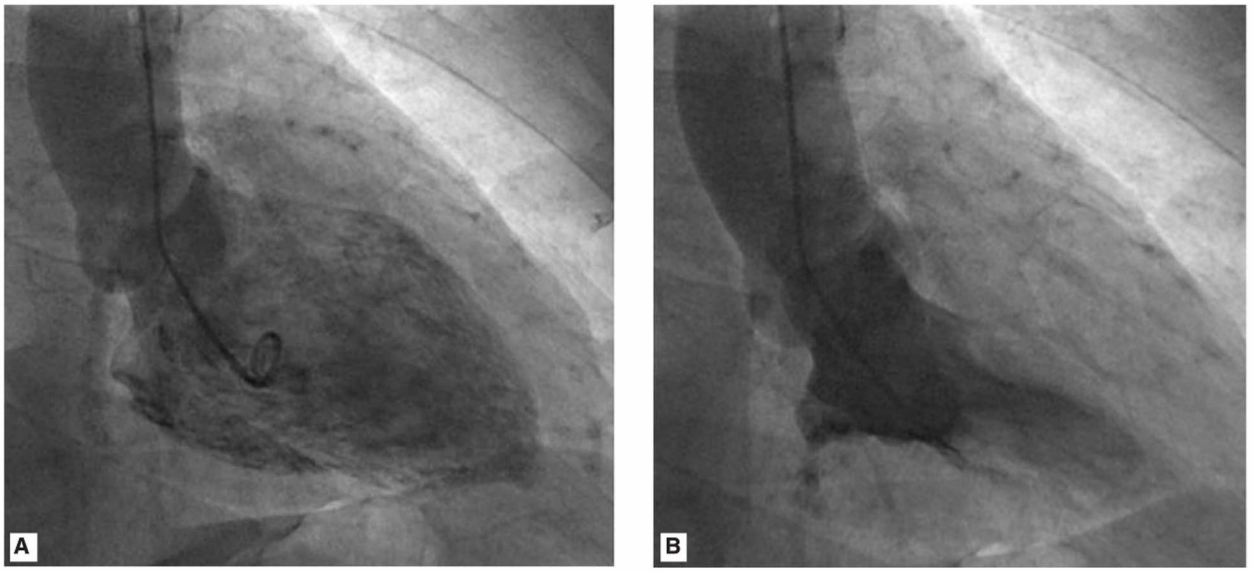



**FIGURE 55-6** Left ventriculography in the right anterior oblique projection shows the left ventricle in (**A**) end diastole and (**B**) end systole. This patient has normal LV systolic function without wall motion abnormalities.

pressures, and RV function. Certain laboratory tests such as natriuretic peptides (BNP and NT-proBNP) should be obtained, especially since elevated levels are associated with high left-sided filling pressures, reduced LV function, ischemia, infarction, and LV hypertrophy.[40] Cardiac catheterization plays an integral role in the evaluation and management of heart failure. A right-heart catheterization provides a measure of cardiac output, right- and left-sided filling pressures, and systemic peripheral resistance. These assessments help to guide the medical management of heart failure. Left-heart catheterization measures LV end-diastolic pressure and left ventriculography provides an assessment of LV systolic function, wall motion abnormalities, and the degree of mitral regurgitation (Figs. 55-6 and 55-7). Furthermore, two-thirds of patients with heart failure and depressed LV function have underlying CAD, and these patients must be evaluated for revascularizable disease. Patients with ischemic chest pain and depressed LV systolic function should be directly referred for coronary arteriography.[40] Surgical revascularization in properly selected patients prolongs survival, improves LV function, and alleviates symptoms.

Several heart failure therapies in addition to revascularization have been shown to improve survival, such as angiotensin converting enzyme inhibitors, β-blockers, aldosterone receptor blockers, and combinations of nitrates and hydralzine in African American patients. Diuretics and digoxin alleviate symptoms, but they do not enhance survival. Although inotropic agents might initially improve performance, they are associated with increased mortality.[40] Devices such as implantable cardioverter-defibrillators and biventricular pacemakers are now recommended to decrease mortality secondary to sudden cardiac death due to ventricular arrhythmias in patients with heart failure and severely depressed LV function.

Cardiac transplantation remains the best treatment for patients with end stage heart failure refractory to optimal medical therapy.[41] Given the limited number of heart donors, the goal is to select patients for transplantation with the greatest likelihood for benefit.[41] Criteria for transplantation include severe refractory heart failure despite maximal medical therapy, markedly impaired hemodynamics, impaired functional capacity (oxygen consumption less that 14 mL/kg/min), refractory angina not amenable to revascularization, congenital disease not suitable for repair, and intractable arrhythmias.[41] Cardiogenic shock, dependence on IV inotropes for adequate organ perfusion, and a peak oxygen consumption of less than 10 mL/kg/min are absolute indications for transplantation in appropriate patients.[40]

Advanced age, severe peripheral vascular disease, irreversible organ (kidney or liver) dysfunction, history of malignancy with likely recurrence, poor medical compliance, active drug abuse, systemic infections, and irreversible pulmonary hypertension are relative contraindications for cardiac transplantation.[41] Advanced age has been associated with worse outcomes following transplantation, and diabetic patients with evidence of neuropathy, nephropathy, and vascular disease are usually considered poor candidates.[41] Irreversible pulmonary hypertension is associated with an increased incidence of death and postoperative complications. In fact, pulmonary vascular resistance greater than 4 Wood units is a contraindication to transplantation, and

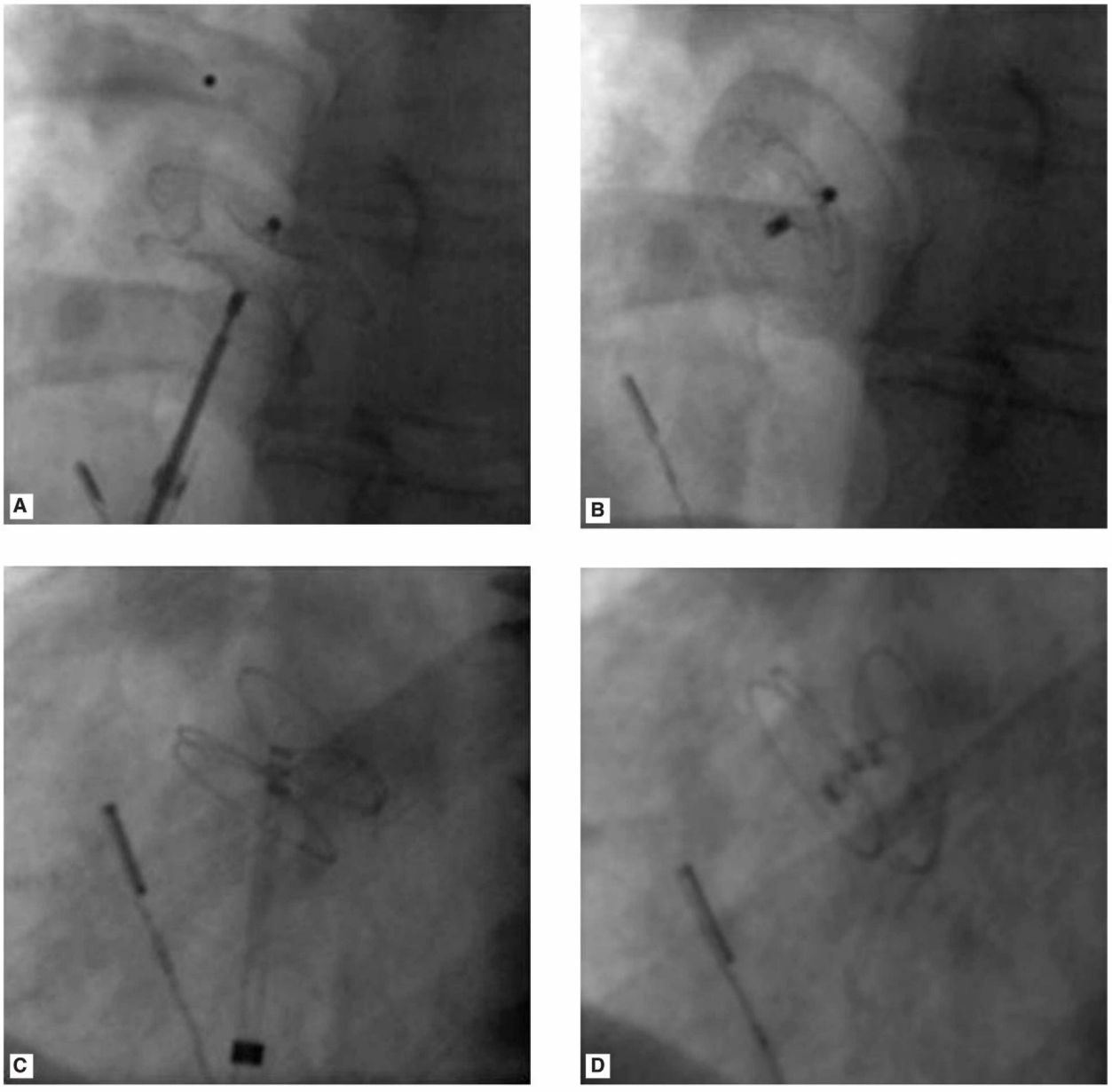



**FIGURE 55-7** **A.** Deployment of Amplatzer septal occluder. **B.** Once the device is stable, it is released by rotating a delivery cable. **C.** HELEX septal occluder prior to and (**D**) after deployment to close a PFO in a patient who suffered a cryptogenic stroke.

pulmonary vascular resistance as expressed in Wood units is calculated by the following formula:

*Pulmonary vascular resistance = (mean pulmonary pressure − PCWP)/cardiac output*

Although cardiac transplantation is available to less than 2500 patients in the United States each year, a left ventricular assist device (LVAD) is a reasonable option as either temporizing or destination therapy in patients with refractory heart failure and a 12-month mortality of 50 percent or less despite optimal medical management.[40]

## PERICARDIOCENTESIS

Pericardial effusions have been treated by percutaneous pericardiocentesis since the 18th century. Percutaneous pericardiocentesis is most commonly indicated for cardiac tamponade

and pericardial effusions greater than 2 cm in diastole.[42] They are also performed for smaller effusions in order to obtain fluid for cytology or culture. The only absolute contraindication for performing a pericardiocentesis is the presence of an aortic dissection, but pericardiocentesis should also not be performed for small, posterior, and/or loculated effusions. Other relative contraindications include traumatic hemopericardium, coagulopathy, and thrombyocytopenia (less than 50,000).[42] The etiologies of pericardial effusion include idiopathic (20 percent of cases), infectious, MI, cardiac surgery, trauma, malignancy, (lung breast cancer, lymphoma), radiation, autoimmune diseases, end stage renal disease, uremia, myxedema, heart failure, and severe pulmonary hypertension.

Percutaneous pericardiocentesis is usually performed in the catheterization lab with fluoroscopy, ECG, and echocardiographic guidance. After the patient is propped up so that the pericardial fluid drains inferiorly, the skin below the xiphoid process is sterilized and anesthetized with lidocaine. A long 18-gauge needle is inserted at a 30° angle to the skin from a subxiphoid approach and is directed toward the left shoulder, avoiding the pleura, coronary, pericardial, and internal mammary arteries. Other approaches may also be used with echocardiographic guidance. A soft J-wire is introduced through the needle, and its position is confirmed with fluoroscopy. Injection of agitated saline through the needle or small bore catheter can be performed with echocardiographic imaging to verify entry into the pericardial space prior to the insertion of a dilator and a multiholed pigtail catheter for drainage. Rapid removal of greater than 1 L of fluid is discouraged to prevent acute dilation of the RV, which is extremely rare.[42] The drainage catheter usually remains in place for 24 to 48 h under slight negative pressure or until the volume is less than 25 mL/day. A stopcock on the end of the catheter should be used for aspiration and flushing to prevent thrombus formation.

Percutaneous pericardiocentesis is associated with a major complication rate of less than 2 percent.[42] Complications include myocardial or coronary perforation (less than 1 percent), arrhythmias, bleeding, pneumothorax, and infection.[42] The most serious complication results from lacerating a coronary artery or from puncturing the LV or RV. Injuring the thin-walled RV is more common than injuring the LV, but it is less dangerous. Puncturing the right atrium is potentially catastrophic but extremely rare.[42] Although fluoroscopically guided pericardiocentesis using the subxiphoid approach remains the standard technique, an echocardiography-guided technique is gaining popularity as it allows for the shortest route to the fluid and has been shown to minimize adverse events.[42]

## ATRIAL SEPTAL DEFECT/PATENT FORAMEN OVALE CLOSURE

An ASD is one of the most common congenital heart anomalies. ASDs have been repaired surgically since 1952 with excellent results. The first attempt at percutaneous closure of an ASD was in the early 1980s, but initially these procedures were limited by high complications rates, a bulky delivery sheath system, and large catheters.[43] Technology has evolved tremendously over the past 2 decades, and newer devices have emerged that markedly improve accessibility and both short- and long-term outcomes. Percutaneous transcatheter closure of secundum ASDs is safe, effective, and reliable and is now preferable over surgical methods.[43] However, proper patient and device selection based on atrial septal anatomy and defect size is essential for successful closure.[43]

Indications for both surgical and percutaneous closure are the same and include a pulmonary-to-systemic shunt ratio ($Q_p/Q_s$) greater than 1.5:1. It is also reasonable to repair defects if the $Q_p/Q_s$ is less than 1.5:1 in the setting of paradoxical emboli, given the procedure's low morbidity and mortality. Closure of a secundum ASD is contraindicated in patients with severe pulmonary vascular disease ($Q_p/Q_s < 0.7:1$).[43]

Approximately 25 percent of adults have a patent foramen ovale (PFO), and the size of the defect increases with age. Although a PFO and secundum ASD are both abnormal communications involving the interatrial septum, they have different etiologies. A PFO is due to incomplete fusion of the septum primum and the septum secundum after birth, while a secundum ASD is the product of a missing segment of the atrial septum secondary to abnormal embryological development. Despite its association with cryptogenic strokes, paradoxical embolization, migraines, platypnea orthodeoxia syndrome, hypoxia with normal pulmonary pressures, and decompression sickness in divers and pilots, PFOs were rarely treated surgically in the past, but these interatrial defects are now being closed percutaneously with excellent procedural success, low complication rates, and low frequency of recurrent events.[43,44]

Although randomized clinical trials of PFO closure to prevent recurrent cryptogenic neurologic events are lacking, there are considerable registry data suggesting that PFO closure decreases recurrent neurologic events compared to medical management. In one study, 110 patients underwent percutaneous closure of a PFO as an alternative to surgery or long-term anticoagulation for prevention of recurrent stroke. Procedural success was 100 percent, and no deaths or strokes occurred during the procedure. The procedural complication rate was 5 percent and included device migration, pericardial tamponade, and arrhythmias.[44] At a mean follow-up of 2.3 years, the annual risk of recurrence was less than 1 percent, and freedom from recurrent cerebral ischemic events and reintervention was 96 and 90 percent at 1 and 5 years, respectively.[44] Although an earlier trial involving PFO closure in 80 patients was successful in 98 percent of the patients, they reported a 10 percent incidence of in-hospital complications.[44] Certainly, percutaneous transcatheter closure of interatrial septal defects involves a steep learning curve, but the complication rate by an experienced interventionalist is as low as 2 percent.[43] Procedural complications of percutaneous PFO and secundum ASD closure include vascular complications, strokes, air embolism, device migration, cardiac perforation, arrhythmias, endocarditis, device thombus, and device fracture.[43]

Percutaneous transcatheter closure of a PFO is an off label use of an FDA-approved device in the absence of randomized controlled trial data comparing medical therapy

to percutaneous closure. According to the American Heart Association, percutaneous closure of a PFO is a class IIB indication in patients with a PFO after a cryptogenic cerebrovascular stroke or after recurrent embolic events despite adequate medical therapy (anticoagulation and therapeutic INR).[43] Previously, the FDA permitted the use of these devices for the prevention of cryptogenic strokes under a Humanitarian Device Exemption based on evidence of device safety and not stroke prevention, but this expired in the end of 2006.[43] The Humanitarian Device Exemption still allows for percutaneous closure of a PFO in the setting of refractory hypoxemia due to right-to-left shunting, but there are no indications for PFO closure in patients with migraines.[43]

Available devices in the United States for percutaneous transcatheter closure of a secundum ASD or a PFO are the Amplatzer atrial septal occluder (ASO) device or cribiform ASD occluder (Amplatzer; AGA Medical, Golden Valley, MN), and the HELEX septal occluder (W.L. Gore and Associates, Flagstaff, AZ). The Amplatzer occluder is a self-expandable, double-disk device composed of nitinol wire and polyester mesh. The ASO device consists of a left atrial disk and a slightly smaller right atrial disk (Fig. 55-7A and B) with a waist that is selected based on balloon sizing of the defect. A cribiform ASO device has equal-sized left- and right atrial discs with a small connecting waist. The ASD closure devices are generally deployed with fluoroscopic and intracardiac echocardiographic guidance. The Amplatzer occluder device is easy to deploy and is self expanding.[43] The Gore HELEX Septal Occluder is made of an ePTFE patch material supported by a nitinol wire frame (Fig. 55-7C and D). Its preassembled delivery system permits deployment of the Helex though an 11F femoral venous sheath. Although the HELEX is approved by the FDA for closure of an ostium secundum ASD up to 18 mm in diameter, the company is presently conducting a randomized, multicenter trial designed to demonstrate the safety and efficacy of the HELEX device in patients with a PFO and a history of either a cryptogenic stroke or a transient ischemic attack. One additional device, the CardioSEAL-STARFlex occluder is an umbrella device supported by one nitinol microspring. The NMT sponsored CLOSURE-1 Study randomized 800 patients with crytogenic stroke to device closure or medical management. This study failed to demonstrate a significant reduction in recurrent neurologic events with PFO closure[45] and consequently PFO closure remains an off-label procedure in the United States. Similar randomized trials are being conducted with the Amplatzer and HELEX devices and hopefully results of these studies will be known in the very near future.

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## CARDIAC CATHETERIZATION AND INTERVENTIONS BOARD REVIEW QUESTIONS (CHAPTER 55)

1. Which of the following statements is true?
   A. A malignancy can occur after a certain threshold of radiation is exceeded.
   B. If the operator stands twice as far away from the source of radiation, he or she decreases his exposure to radiation by half.
   C. Pregnant lab personnel must not be exposed to fluoroscopy.
   D. The maximum amount of whole body radiation dose per year is 5 rems.
   E. The maximum amount of whole body radiation dose per lifetime is 100 rems.

2. Which if the following statements is false?
   A. The ostium of the LM is best seen in the LAO or LAO cranial projection.
   B. The distal LM is best seen in an AP or shallow RAO caudal view.
   C. The LCx is best visualized in the RAO or LAO caudal projection.
   D. The mid-to-distal LAD is best visualized in the LAO caudal projection.
   E. The ostium of the RPDA is best seen using a shallow RAO view.

3. Which of the following is an indication for percutaneous balloon aortic valvulopasty?
   A. Bridge to surgery in an unstable patient with severe aortic stenosis and heart failure
   B. Octogenarians or nonagenarians who have severe aortic stenosis
   C. Palliation in a patient with critical aortic stenosis who is not a surgical candidate due to multiple comorbidities
   D. A and C
   E. All of the above

4. Which of the following treatments has not been shown to improve survival in patients with heart failure?
   A. Surgical revascularization
   B. Angiotensin converting enzyme inhibitors
   C. Dobutamine
   D. β-Blockers
   E. None of the above

5. Which of the following is an FDA-approved indication for percutaneous PFO closure?
   A. Cryptogenic strokes or paradoxical emboli
   B. $Q_P/Q_s$ >1.5:1
   C. Cryptogenic stroke and $Q_P/Q_s$ >1.5:1
   D. All of the above
   E. None of the above

## ANSWERS

1. **Answer: D.** The maximum amount of whole body radiation dose per year is 5 rems. The other statements are false.
2. **Answer: D.** The mid-to-distal LAD is best visualized in the RAO and LAO cranial projections. The other statements are true.
3. **Answer: D.** BAV is a reasonable option in unstable patients who are at too high risk for aortic valve replacement or as a bridge to surgery. Valvuolplasty should not be substituted for valve replacement in elderly patients if they are suitable surgical candidates and lack multiple comorbidities.
4. **Answer: C.** Inotropic agents such as milrinone and dobutamine have actually been shown to increase mortality.
5. **Answer: E.** Closing a PFO percutaneously is an off-label use of an FDA-approved device.

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56

# Echocardiography in Cardiac Surgery

*Colleen Harrington*
*Samia Mora*
*Katherine C. Wu*

## PRINCIPLES OF ECHOCARDIOGRAPHY

Since 1976, echocardiography (echo) has been used to evaluate cardiac structure and function. Echo uses sound in the high-frequency range (2–10 MHz). Frequency ranges between 2 and 5 MHz are typically used for imaging adults, while frequencies of 7.5 to 10 MHz are used for children and specialized adult applications. The transducer contains a piezoelectric crystal that converts electrical to sound energy, producing sound waves that are transmitted in the form of a beam. A complete transthoracic echocardiogram (TTE) consists of a group of interrelated applications including two-dimensional (2D) anatomic imaging, M-mode, and three Doppler techniques: pulsed-wave (PW), continuous-wave (CW), and color-flow (CF) imaging.[1–7] In addition, the quantification of cardiac chamber dimensions, areas, and volumes is an important aspect of a complete examination. Using a combination of these ultrasound techniques, one can assess the anatomy and function of the cardiac valves, myocardium, and pericardium.

## TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Standard views are obtained along three orthogonal planes of the left ventricle (LV): long-axis, short-axis, and the four-chamber plane (Fig. 56-1A–C). The long axis is parallel to the long axis of the LV. The short axis cuts the LV cross-sectionally, similar to slices of bread in a loaf, and is orthogonal to the long axis. Four standard transducer locations are used to obtain complete visualization of the entire heart: parasternal, apical, subcostal, and suprasternal.

## M-MODE ECHOCARDIOGRAPHY

M-mode is a one-dimensional "ice pick" view of the heart (Fig. 56-1D) and is often used for measuring LV systolic and diastolic chamber dimensions and wall thickness.

## DOPPLER ECHOCARDIOGRAPHY

The Doppler effect is the phenomenon whereby the frequency of sound waves increases or decreases as the sound source moves toward or away from the observer. The resultant Doppler frequency shift can be detected and translated into blood-flow velocity. The velocity of blood can then be used to calculate valvular gradients and areas, intracardiac pressures, and volumetric flow.

### Pulsed-Wave Doppler

Pulsed-wave (PW) Doppler is obtained when a pulse of ultrasound is transmitted intermittently, allowing for estimation of blood-flow velocity at a specific region of interest. It is thus "site-specific." Its disadvantage is aliasing (or wrap-around) of the signal at velocities that are one-half of the pulse repetition frequency (Nyquist limit). This property limits the maximal velocity that can be accurately measured with PW.

### Continuous-Wave Doppler

Continuous-wave (CW) Doppler records all the velocities along the path of the ultrasound beam. Using CW, the magnitude of the blood-flow velocity and its direction can be accurately recorded. Its disadvantage is that it does not allow localization of the specific site of the velocity obtained along the beam path. CW is used to measure high-velocity jets associated with valvular dysfunction as well as intracardiac pressure gradients. The simplified Bernoulli equation can then be used to convert velocities into pressure gradients ($\Delta P = 4V^2$).

### Color-Flow Doppler

Color-flow (CF) Doppler transforms Doppler velocity information into a color-coded scheme. Red denotes flow

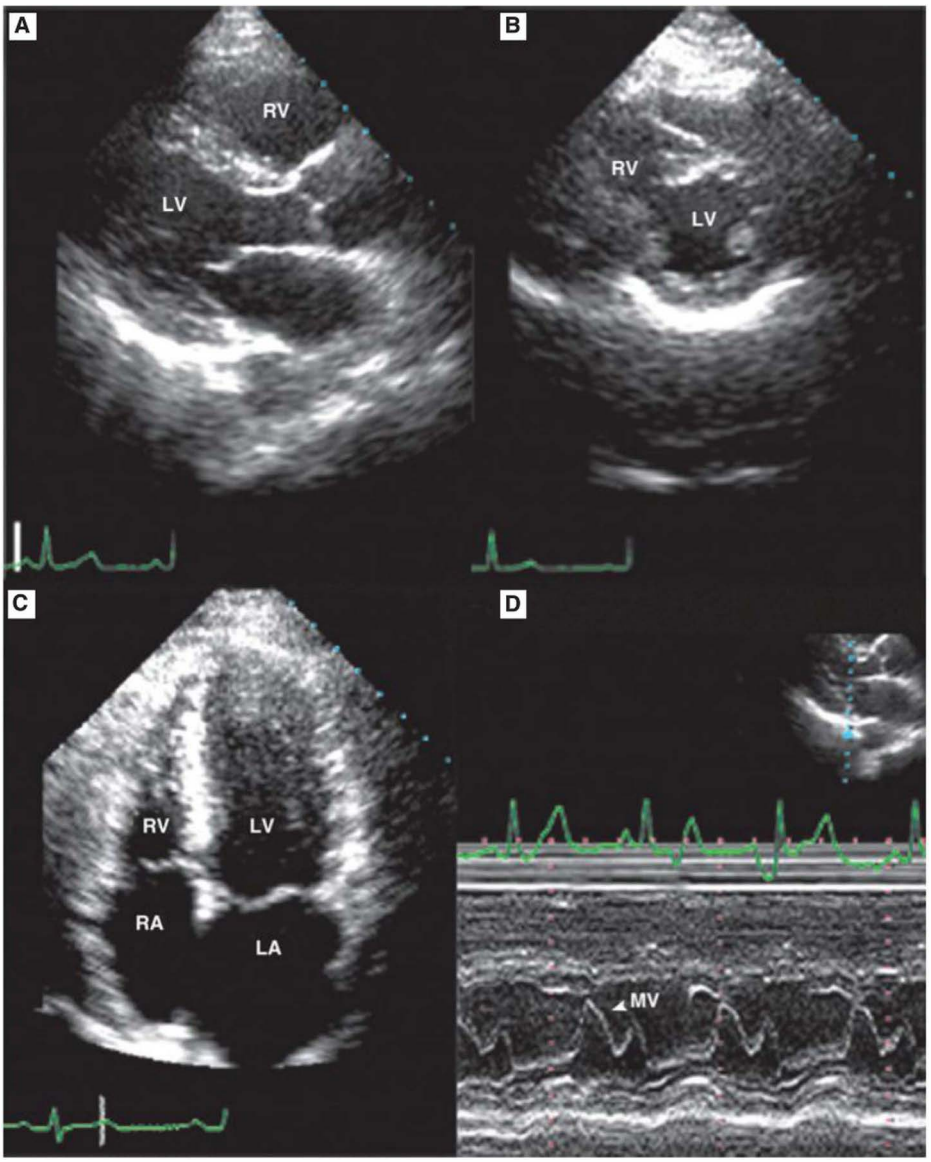



**FIGURE 56-1** Standard 2D TTE (**A–C**) and M-mode (panel **D**) views in a normal individual. **A.** Parasternal long-axis view of the right ventricle (RV), interventricular septum, left ventricle (LV) cavity and posterior wall, and both mitral and aortic valves. Since the RV is the most anterior structure, it will be located closest to the transducer beam and is seen at the top of the image display, while the LV and LA (both posterior structures) are farther away from the transducer and are seen at the bottom of the image. **B.** Parasternal short-axis view of the ventricles at the papillary muscle midventricular level obtained by rotating the transducer 90 degrees. **C.** Apical four-chamber view, important for evaluation of ventricular function, apical thrombus, mitral and tricuspid valve function. **D.** M-mode view through the RV and mitral leaflets. This view is useful for detecting RV diastolic collapse in tamponade.

toward the transducer, while blue represents flow away from the transducer. The relative velocity of blood flow is also depicted, with brighter shades of blue or red representing higher velocities. Turbulent flow is seen as multicolored jets (e.g., due to valvular disease or intracardiac shunts).

## TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Transesophageal echocardiography (TEE) was first introduced clinically in the United States in the 1980s. By placing an echocardiographic probe in the esophagus, the

distance between the transducer and the structures of interest is decreased. This allows the use of higher frequency (5- and 7-MHz) transducers that further enhances image quality[39]. The development of transducer crystals that rotate from 0 to 180 degrees also allows for examination of each cardiac structure from different planes and angles. Acquisition of images is from two basic locations: midesophageal (30–35 cm from the incisors) and midgastric (40–45 cm from the incisors).

## Indications

Typically, a TEE examination provides additional information but does not replace a transthoracic examination. In the evaluation of the anterior structures, a TTE may in fact provide better image quality. A TEE is useful for the evaluation of patients with limiting body habitus, such as obesity or emphysema, who are not optimally imaged by the transthoracic approach. In addition, certain structures that are not well visualized by TTE [such as the left atrial (LA) appendage, thoracic aorta, and prosthetic valves] can be assessed by the transesophageal approach. A third common indication is to guide intraoperative management during cardiac surgery. Class I indications for perioperative TEE (conditions for which there is evidence and/or general agreement that TEE is useful and effective) are listed in Table 56-1.[8] There are other situations in which TEE may also be useful but is not required (i.e., class II indications: conditions in which there is a divergence of opinion about the usefulness/efficacy of a procedure but in which the weight of opinion is in favor of usefulness/efficacy). These include ongoing surgical procedures in patients at increased risk of myocardial ischemia or hemodynamic instability, minimally invasive surgery, or intracardiac mass resection. Examples include, the Cox-Maze procedure, cardiac tumor resection, aneurysmorrhaphy, intracardiac thrombectomy, and pulmonary embolectomy.

**TABLE 56-1: Class I Indications for Perioperative TEE**

| |
|---|
| Acute and life-threatening hemodynamic instability |
| Valve repair or complex valve replacements |
| Hypertrophic obstructive cardiomyopathy |
| Aortic dissection with possible aortic valve involvement |
| Endocarditis (perivalvular involvement) |
| Congenital heart surgery |
| Pericardial windows (posterior or loculated effusions) |
| Placement of intracardiac devices |

Data modified from Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: Summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *Circulation* 2003;108:1146–1162.

It is also particularly useful in detecting intracardiac air or aortic atheromatous disease and for selecting anastomotic sites during heart/lung transplantation.[8] Antibiotic prophylaxis for infective endocarditis is usually unnecessary but is optional in the high-risk patient (e.g., complex congenital heart disease, prosthetic valve, poor dentition, or prior history of endocarditis).[9]

## Contraindications and Complications

Relative contraindications for TEE include significant esophageal pathology (e.g., strictures, varices), history of radiation therapy to the mediastinum, and recent esophageal or gastric surgery. Serious complications of TEE are uncommon (<1 percent) but may include aspiration and other problems related to sedation, mucosal trauma, laryngospasm, esophageal or pharyngeal laceration or perforation, methemoglobinemia, and rarely death. Death occurs in less than 1 in 10,000 patients. The passage of the TEE probe is "blind" and is done without direct visualization. The severe complications of esophageal or pharyngeal trauma are signaled by patient complaints of severe pain and inability to swallow, which usually occur after the procedure has ended and sedation has worn off. Esophageal perforation during intraoperative TEE can go undetected for a period of time because of the use of anesthesia and paralytics that prevent patient feedback regarding pain during probe passage.

# THREE-DIMENSIONAL ECHOCARDIOGRAPHY

Three-dimensional (3D) echocardiography has been one of the most important developments in cardiac ultrasound imaging during the last decade. Cardiac structures are seen in relation to each other in all three spatial dimensions[39]. Acquisition of data includes volumetric ultrasound imaging. It also includes 2D imaging in multiple planes with a known 3D location; as long as the images are linked. 3D echocardiography has been shown to be more accurate in the measurement of LV volumes and ejection fraction (EF) and has been validated against accepted reference techniques such as cardiac magnetic resonance[40]. 3D echocardiography is not widely available yet and it not part of the routine clinical examination.

# ASSESSMENT OF VENTRICULAR FUNCTION

Routinely, a qualitative visual estimate of global LV systolic function is obtained by examining LV wall thickening and motion in multiple topographic planes. It is imperative that the endocardium is visualized to make this assessment. In addition, LV systolic function can also be assessed semiquantitatively by using a grading scale (wall

motion score). On TEE, images obtained from the esophagus and transgastric orientations are used to assess LV systolic function.

## LEFT VENTRICULAR EJECTION FRACTION

EF is often reported qualitatively as increased (hyperdynamic), normal, mildly, moderately, or severely reduced.[8] In addition, the reader often assigns an estimated value to the qualitative assessment. Normal LV EF is 61 ± 10 percent.[10]

Visual estimation of EF by experienced readers is generally reliable but is limited by reader variability and depends on optimal echocardiographic delineation of the endocardium.

EF can also be quantified from the equation below after determining end-diastolic volume (EDV) and end-systolic volume (ESV):

$$EF = SV/EDV = (EDV - ESV)/EDV$$

where SV, stroke volume; EDV, end-diastolic volume; and ESV, end-systolic volume.

Volumes can be obtained by the modified Simpson's rule or method of disks. This calculates ventricular volume as the sum of parallel slices from the apex to the base. Further details of the technique can be found in several of the references.[1,2,11]

## LEFT VENTRICULAR FRACTIONAL SHORTENING (PERCENT FRACTIONAL SHORTENING)

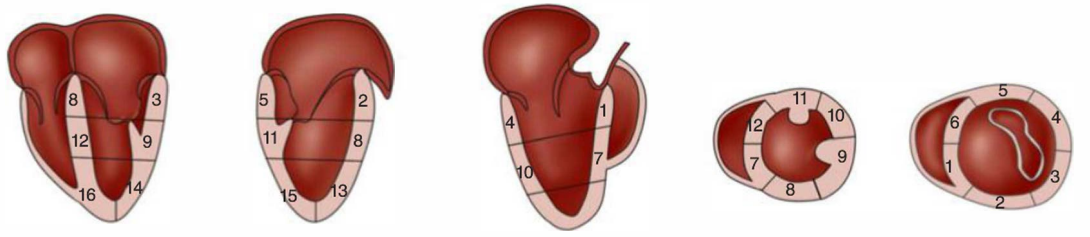
Percent FS is another method for estimating LV systolic function and reflects a percent change in LV dimension with systolic contraction. It is calculated from LV end-diastolic and end-systolic dimensions measured by M-mode. The normal range for FS is between 25 and 45 percent. For ventricles that are roughly symmetrical without regional wall motion abnormalities, EF is approximately 2 (percent FS).

$$\text{Percent FS} = (EDD - ESD) / EDD \times 100$$

where EDD, end-diastolic dimension and ESD, end-systolic dimension.

## LEFT VENTRICULAR REGIONAL WALL MOTION

For the assessment of LV regional wall motion, the LV is divided into 16 segments (Fig. 56-2), each of which is given a score from 1 to 5 (1, normal or hyperkinetic; 2, hypokinetic; 3, akinetic; 4, dyskinetic; 5, aneurysmal or diastolically deformed). This grading system differs from the 1-to-5 grading system of TEE often used by cardiac anesthesiologists [1, normal (>30 percent thickening); 2, mildly hypokinetic (10–30 percent thickening); 3, severely hypokinetic (<10 percent thickening);




Four-chamber view | Two-chamber view | Long-axis view | Mid-short-axis view | Basal short-axis view

| Basal segments | Mid segments | Apical segments |
|---|---|---|
| 1 = Basal anteroseptal | 7 = Mid anteroseptal | 13 = Apical anterior |
| 2 = Basal anterior | 8 = Mid anterior | 14 = Apical lateral |
| 3 = Basal lateral | 9 = Mid lateral | 15 = Apical inferior |
| 4 = Basal posterior | 10 = Mid posterior | 16 = Apical septal |
| 5 = Basal inferior | 11 = Mid inferior | |
| 6 = Basal septal | 12 = Mid septal | |

**FIGURE 56-2** Sixteen-segment model of the left ventricle. According to guidelines of the American Society of Echocardiography and the Society of Cardiac Anesthesia, the left ventricle is divided into 16 segments (6 basal, 6 midventricular, and 4 apical segments) for evaluation of wall motion and calculation of the wall motion score. (From Shanewise JS, Cheung AT, Aronson S, et al. ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: Recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. *J Am Soc Echocardiogr* 1999;12:884–900. With permission. Copyright Elsevier.)

4, akinetic (no thickening); 5, dyskinetic (paradoxical systolic motion)].[12] The wall motion score index is calculated as the sum of segmental wall motion scores divided by the number of segments seen. A score of 1 is normal, and higher wall motion scores indicate more extensive ventricular dysfunction. However, this grading system is more useful for research databases than for clinical use.

## LEFT VENTRICULAR FILLING

LV preload is the LV volume at end-diastole. Normal LV end-diastolic size is 3.5 to 5.7 cm in the parasternal long-axis view. The size of the ventricles and atria may be used for the qualitative evaluation of filling pressures and assessment of hyper- or hypovolemia, particularly intraoperatively with TEE.[13] Small LA size and near cavity obliteration of the LV can indicate hypovolemia.[14] On the other hand, ventricular and atrial enlargement may indicate hypervolemia or an underlying cardiomyopathy. Doming of the interatrial septum toward the right suggests elevated LA pressure and increased LV preload. One limitation to using TEE for indirect measurement of volume status is that the LV may be foreshortened; it is therefore recommended that the LV be imaged from several different planes to get a more accurate estimate of LV volume.[14]

## LEFT VENTRICULAR DIASTOLIC FUNCTION

Doppler echo is the most common diagnostic tool for assessing diastolic function. Indices of transmitral and pulmonary venous Doppler flows are commonly used to identify patterns of diastolic dysfunction.[11]

### Mitral Valve Inflow

When sinus rhythm is present, PW Doppler at the level of the mitral valve (MV) leaflets records two velocities separated by a period of diastasis (no flow), as shown in Fig. 56-3. After the MV opens, early rapid diastolic filling of the LV occurs (E wave), followed by a period of diastasis, after which late filling occurs due to atrial contraction (A wave). Normally, in individuals less than 60 years old, the peak *E*:*A* wave velocity ratio is greater than 1. When there is impaired relaxation without elevated filling pressures, the peak E decreases; hence, the *E*:*A* ratio becomes less than 1. In contrast, a "restrictive" filling pattern is seen when both impaired relaxation and elevated filling pressures are present, resulting in a smaller contribution of atrial contraction and an increased *E*:*A* ratio (>1.5–2).

### Pulmonary Vein Flow

Four velocities are seen in PW Doppler of the pulmonary veins (Fig. 56-4). Occurring in early systole, the first systolic forward flow velocity ($PV_{S1}$) is due to the relaxation of the LA,

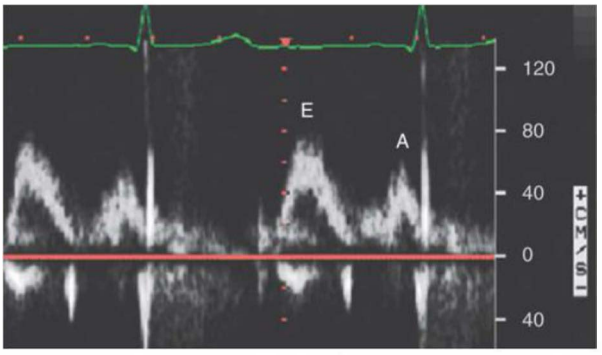



**FIGURE 56-3** Pulsed-wave (PW) Doppler of the mitral valve inflow. This figure shows a normal pattern of blood flow through the mitral valve in diastole. The two peaks indicate early (E wave) and late (A wave) diastolic filling separated by a brief period of diastasis (no flow). In individuals less than 65 years old, a normal *E*:*A* ratio is 2:1. Deceleration time is the time interval from peak E velocity to baseline.

which promotes pulmonary venous flow into the LA. In mid-to-late systole, a second systolic forward flow ($PV_{S2}$) occurs that is produced by the increase in pulmonary venous pressure occurring after right ventricular (RV) systole. In diastole, a third pulmonary vein velocity is seen ($PV_D$). This is related to the decrease in LA pressure seen after MV opening. The fourth velocity is the atrial flow reversal velocity ($PV_a$) that is related to LA contraction. A pulmonary vein systolic velocity peak less than the diastolic velocity peak is suggestive of elevated LA pressures. Restrictive filling indicative of very high filling pressures is seen when $PV_{S2}$ is much less than $PV_D$. When higher filling pressures are present, both the duration and peak velocity of $PV_a$ are increased. Another sign of elevated LA pressure is when the duration of $PV_a$ is longer than the duration of the mitral inflow A wave (by >0.03 s).

## RIGHT VENTRICULAR SIZE, FUNCTION AND FILLING PRESSURES

Qualitative evaluation of RV size, wall thickening, and motion is done visually. The subcostal and apical four-chamber views provide the most accurate assessment of RV size. Normal RV size is less than two-thirds of LV size (see Fig. 56-1) and wraps around the LV in a U-shaped manner. The RV size is described as normal if it smaller than the LV and its apex is more basally located than the LV apex; mildly dilated if it is enlarged but to a lesser extent than the LV area; moderately dilated if the RV area is the same as the LV area; and severely dilated if the RV area is larger than the LV. RV hypertrophy is present when the RV free wall thickness is >0.5 cm.

Assessment of RV function is also done visually as is estimation of LV function; however, it is much more difficult to estimate RV function. The function is compared to the function of the LV and is described as normal, mildy reduced, moderately reduced, and severely reduced. It can also be assessed by the amount of displacement of the tricuspid valve

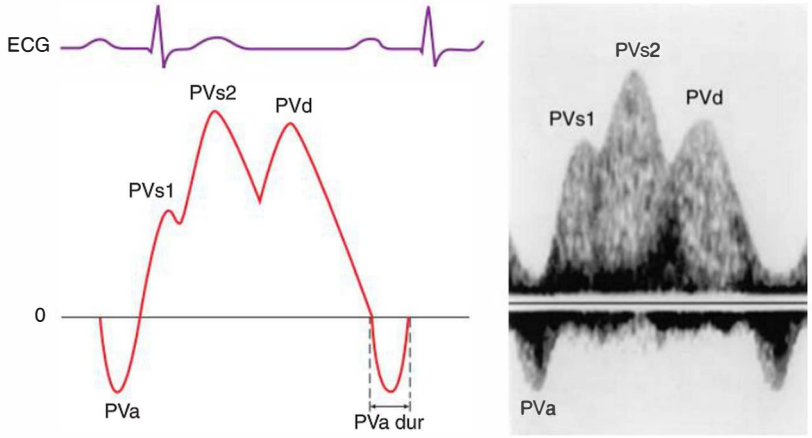



**FIGURE 56-4** Pulsed-wave (PW) Doppler of the pulmonary vein. This figure shows a normal pattern of blood flow through the pulmonary veins with four velocities seen ($PV_{S1}$, $PV_{S2}$, $PV_{D}$, $PV_{a}$). Duration of peak reverse flow velocity during atrial contraction ($PV_{a}$ dur) is also measured. (From Oh JK, Appleton CP, Hatle LK, et al. The noninvasive assessment of left ventricular diastolic function with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 1997;10:246–270. With permission. Copyright Elsevier.)

annulus toward the apex in systole. A reduction of motion of less than 1.5 cm indicates a significant reduction in RV function. Normal tricuspid annular motion is 1.5 to 2.0 cm.

Septal wall flattening (resulting in a D-shaped LV in the short-axis view) or septal deviation into the LV can be seen in both pressure- and volume-overload conditions of the RV.[12] With elevated RV pressure, the septum moves toward the LV with maximum reversed curvature in midsystole. In RV volume overload, the reversed curvature of the septum is seen in middiastole with normalization during systole.

When tricuspid regurgitation (TR) is present, the RV systolic pressure (RVSP) can be estimated (see also "Pulmonary Hypertension," below). TTE is preferred to TEE for measuring RVSP because of better alignment of the transducer beam with the direction of the regurgitant jet.

Examination of the size and respiratory changes of the venae cavae and hepatic veins can give helpful clues to the patient's volume status and is also used in the evaluation of pericardial disease. Although TTE is preferred for examination of the respiratory variation of the inferior vena cava (IVC), TEE provides better visualization of the superior vena cava. Dilatation of the superior vena cava (greater than one-half the aortic dimension in the short-axis view) is suggestive of hypervolemia.[14]

# VALVULAR DISEASE

## Mitral Valve

### MITRAL VALVE MORPHOLOGY

Normal MV function depends on the normal function of all its component parts, including the mitral leaflets, annulus, chordae tendineae, and papillary muscles. Not only is LV function important for normal MV function but also the cavity size, since LV dilation will prevent or limit leaflet coaptation in systole, causing mitral regurgitation (MR). The rectangular posterior leaflet is composed of three scallops (P1, P2, P3), while the semicircular anterior leaflet is divided into thirds for descriptive purposes (Fig. 56-5). Normal MV area is 4 to 6 $cm^2$.

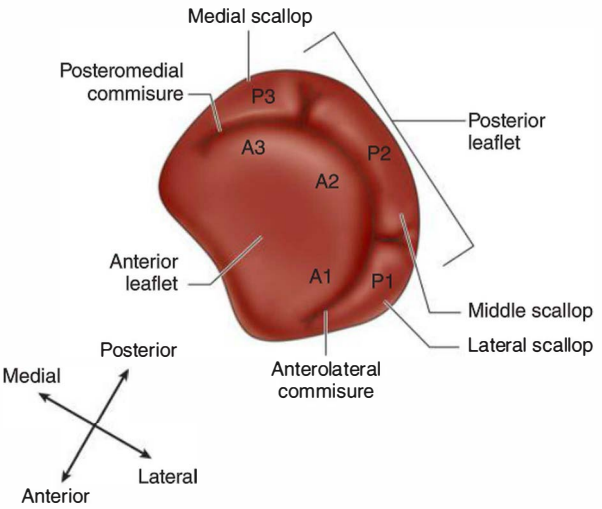



**FIGURE 56-5** Mitral valve structure. The mitral valve consists of two leaflets, the anterior and posterior leaflets, which are separated at the annulus by the posteromedial and anterolateral commissures. The posterior leaflet is rectangular and composed of three scallops (P1, P2, P3). The anterior leaflet is semicircular and is divided into three segments for descriptive purposes (A1, A2, A3). (From Shanewise JS, Cheung AT, Aronson S, et al. ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: Recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. *J Am Soc Echocardiogr* 1999;12:884–900. With permission. Copyright Elsevier.)

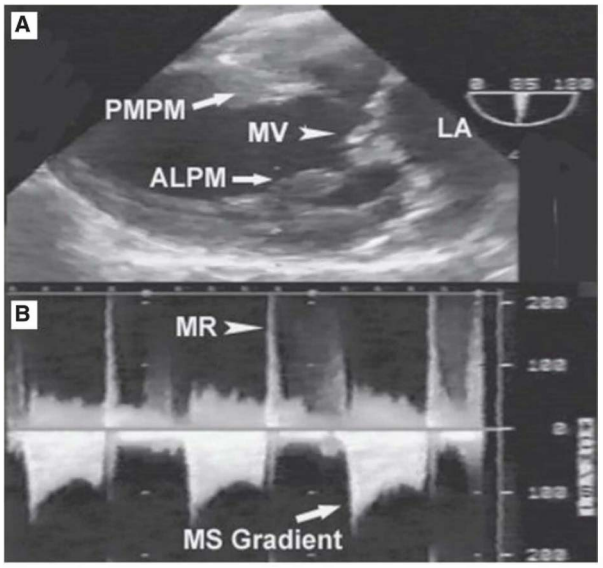



**FIGURE 56-6** Rheumatic mitral stenosis. **A**. Transesophageal transgastric long-axis view of the left ventricle, the anterolateral papillary muscle (ALPM), the posteromedial papillary muscle (PMPM), mitral valve (MV) leaflets, and left atrium (LA). Note the thickened and partially calcified subvalvular and valvular structures (short arrow). The patient had severe three-vessel coronary artery disease in addition to rheumatic aortic stenosis and atrial fibrillation and underwent successful mitral and aortic valve replacements and coronary artery bypass grafting. **B**. Continuous-wave (CW) Doppler of the mitral valve intraoperatively. MR, mitral regurgitation; MS, mitral stenosis.

## MITRAL STENOSIS

Rheumatic heart disease is the most common cause of mitral stenotic lesions (Fig. 56-6), with leaflet thickening and fusion of the commissures. Subvalvular involvement is also common, which causes chordal thickening, shortening, calcification, and fibrosis. This creates the characteristic fish-mouth valve that is best seen in the short-axis view. Commissural fusion results in bowing of the leaflets in diastole causing a hockey-stick appearance in the long-axis view.

2D echo is the "gold standard" for evaluating mitral stenosis (MS) and allows assessment of the structure and function of the mitral annulus, leaflets, chordae, papillary muscles, LV size and function, LA size, and pulmonary hypertension (RVSP). 2D short axis imaging during diastole allows assessment of the valve area that has been well validated with measurements obtained intraoperatively. The Wilkins echo score[15] for rheumatic MS is based on four variables (leaflet mobility, leaflet thickening, subvalvular thickening, and calcifications). Each variable receives a score of 1 to 4 and the individual scores are summed up. A total score equal to or greater than 8 is associated with better outcomes for mitral balloon valvuloplasty. For valves with less favorable scores (>8), cardiac surgery with valve replacement may be the preferred treatment option.

***Mitral Valve Area.*** As mentioned above, the 2D short axis imaging on TTE allows direct planimetry of valve area. With this approach, it is important to scan completely above and below the MV plane in order to identify the smallest orifice. Direct planimetry is difficult if image quality is poor.

Calculation of MV area can be done by using the pressure half-time (PHT) method. PHT is the time (milliseconds) for the maximal pressure gradient to decrease by half and is usually equal to the deceleration time multiplied by 0.29.

$$\text{MV area (cm}^2\text{)} = 220/\text{PHT (ms)}$$

Accurate assessment of MV area requires a near-parallel orientation between directions of blood flow and the Doppler beam. The PHT method has several important shortcomings. It is affected by concomitant aortic regurgitation (AR) or decreased LV compliance.[4] Rapid increase in LV diastolic pressure associated with either of these conditions may shorten the PHT and underestimate the extent of stenosis. Severe AR can actually lead to restricted opening of MV leaflet causing functional MS and lengthening of the PHT measurement in addition to anatomic stenosis. Another technique to estimate valve area includes the continuity equation.[1,4] The latter approach is also less reliable in the presence of significant aortic and MR. Details of this approach are outlined in references 1 through 11.

***Mitral Valve Pressure Gradients.*** As the degree of obstruction to blood flow caused by a stenotic valve increases, the velocity of the blood flow also increases in order to maintain constant flow (conservation of mass or flow). Velocities can then be transformed into pressures with the simplified Bernoulli equation:

$$\Delta P = 4V^2$$

where $\Delta P$, MV pressure gradient (mm Hg) and $V$, velocity of blood flow across the MV (ms).

***Severity of Mitral Stenosis.*** The mean MV pressure gradient and MV area are used to estimate the severity of MS and the need for intervention (Table 56-2).

**TABLE 56-2: Severity of Mitral Stenosis**

| Severity | Mitral Valve Area (cm²) | Mean Gradient[a] (mm Hg) |
|---|---|---|
| None | 4–6 | – |
| Mild | 1.6–2.0 | <5 |
| Moderate | 1.1–1.5 | 5–10 |
| Severe | ≤1 | >10 |

[a]Assumes normal cardiac output.

Reproduced from ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease. A report of the American College of Cardiology/American Heart Association. Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *J Am Coll Cardiol* 1998;32:1486–1588. Copyright Elsevier.

## MITRAL REGURGITATION

There are three basic mechanisms of MR: primary abnormalities of the mitral leaflets, commissures, or annulus; malfunctioning of the subvalvular structures (chordae tendineae and papillary muscles); and alterations in LV and LA dimensions and function.

The most common cause of isolated severe MR is myxomatous degeneration (Fig. 56-7). The valve itself can also be deformed from rheumatic fever, mitral annular calcification, infective endocarditis, and congenital lesions (cleft MV). Myxomatous degeneration is appreciated by thickened, redundant leaflets and chordae that exhibit excessive motion. The leaflets prolapse into the left atrium in systole. The severity ranges from mild prolapse to severe prolapse or a flail leaflet. Mitral annular calcification is seen more commonly in elderly patients and in patients with renal disease

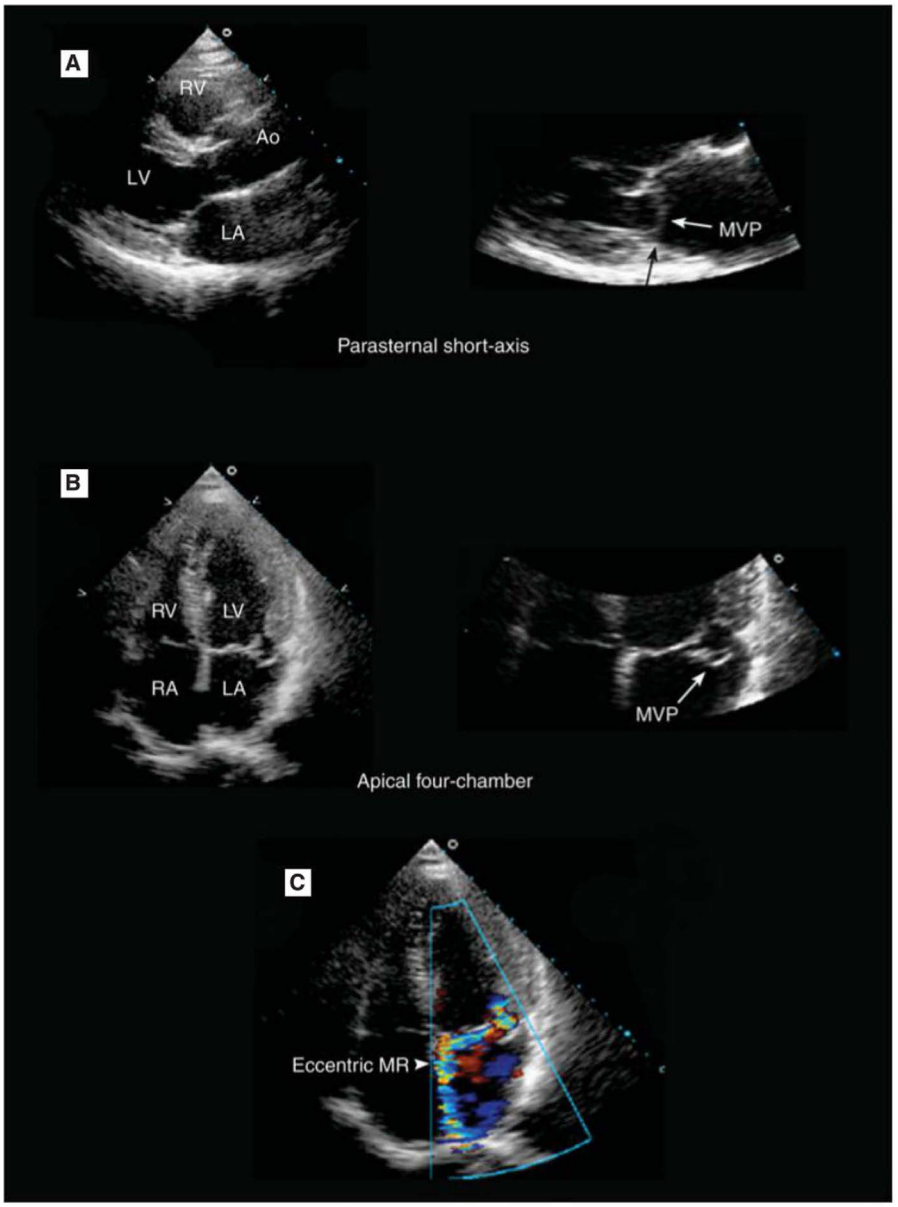



**FIGURE 56-7** Myxomatous mitral valve prolapse and mitral regurgitation. **A.** Transthoracic parasternal long-axis view of the mitral valve with a greater than 2-mm prolapse of the posterior leaflet (MVP) beyond the plane of the annulus. **B.** Apical four-chamber view shows biatrial enlargement. **C.** Color-flow Doppler shows severe mitral regurgitation (MR) with an eccentric jet that is "wall hugging" and anteriorly directed (opposite the side of leaflet prolapse).

and more commonly affects the posterior annulus. It is exhibited by increased echogenicity and subsequent acoustic shadowing.

Other less common causes of leaflet abnormalities include endomyocardial fibrosis, carcinoid disease, drugs (e.g., fenfluramine hydrochloride and phentermine, or Fen-Phen), radiation therapy, trauma, Marfan disease and collagen vascular disease.

Abnormalities in the subvalvular structures include dysfunctional and/or ruptured chordae tendineae and papillary muscles. Ruptured chordae tendineae accounts for a large proportion of MR lesions. Etiologies include idiopathic causes, MV prolapse, infective endocarditis, and thoracic trauma. Papillary muscle dysfunction (with or without frank rupture) is most often seen in the setting of myocardial ischemia or infarction. The posteromedial head of the papillary muscle is most vulnerable to ischemia because of its end-artery vascular supply. Ischemic MR causes restricted leaflet motion resulting in the tenting of the MV in systole. Other causes of dysfunction include dilated cardiomyopathy, myocarditis, hypertension, and chest trauma. Papillary muscle partial or complete rupture is a known potential complication of a myocardial infarction. The ruptured papillary muscle head is visualized in the left atrium in systole and in the LV in diastole.[40]

Global or regional LV enlargement may dilate the mitral annulus and change the position and axis of contraction of the papillary muscles, leading to dysfunction. This is often called functional MR. Progressive LA and LV enlargement associated with chronic MR further exacerbate the extent of MR because of continued changes in chamber geometry.

***Two-Dimensional Echocardiography.*** Unlike the case in MS, where echo is the accepted gold standard for diagnosis, there is no gold standard for the assessment of MR; therefore, multiple parameters are used in estimating the severity of MR.[16] The purpose of echo in MR is to determine the etiology, mechanism, and severity of regurgitation; determine the need and type of surgery; and evaluate other valves, RV and LV function, and the presence of pulmonary hypertension. The most important aspect is to determine the hemodynamic significance of the regurgitation based on LV size (particularly end-systolic dimension), LV systolic function (EF), and the presence and degree of LA enlargement and pulmonary hypertension (RVSP). Regurgitant jet size and area may contribute to the assessment of MR but often correlate poorly with MR severity.[16] The degree of MR intraoperatively may appear less or more severe compared to the degree preoperatively, because of different hemodynamic and ischemic conditions (e.g., lower blood pressure or relief of ischemia will reduce the amount of regurgitation).[17]

***Echocardiographic Findings in MR.*** MR results in LV volume overload. Acutely, the LV is able to empty more efficiently, such that forward cardiac output is maintained. Chronic MR leads to LV dilation and eventual decrease in contractility. The LA also increases in size to accommodate the regurgitant volume. Pulmonary artery pressures increase both in acute MR as well as in chronic MR due to elevated LA pressures. This can subsequently lead to pulmonary hypertension. The direction and shape of the regurgitant jet may aid in assessment of valve pathology and severity. Anterior leaflet pathology produces a posteriorly directed jet and posterior leaflet pathology causes an anterior directed jet. A central jet is often seen in dilated cardiomyopathy as mentioned earlier due to a dilated LV and/or valve annulus.[40]

***Severity of Mitral Regurgitation.*** Echo findings in severe MR[4,16] include the following:

- Large regurgitant jet: >40 percent of LA area.
- Wide vena contracta (the narrowest part of the regurgitant color jet at its origin): ≥7 mm.
- Eccentric wall-impinging regurgitant jet (Fig. 56-7B).
- Dilated LV: end-systolic dimension ≥45 mm or end-diastolic dimension ≥70 mm.
- LV EF <55 to 60 percent.
- Dilated LA (≥5.5 cm), although the LA may not be dilated in acute MR.
- Pulmonary hypertension: resting RVSP >50 mm Hg.
- Restrictive mitral filling pattern: high peak early transmitral velocity (E wave) >1.5 ms.
- Pulmonary vein systolic flow reversal: A normal pulmonary vein Doppler pattern has a systolic (S) wave larger than the diastolic (D) wave. As the MR progresses, the S wave decreases until it may become reversed. While a reduced S wave is a nonspecific finding,[18] the presence of a reversed S wave has high specificity for significant MR. The absence of a reversed S wave does not exclude significant MR.
- Effective orifice area (ERO) ≥0.4 $cm^2$.

Table 56-3 summarizes the important echo features of MV stenosis and regurgitation.

**TABLE 56-3: Echocardiographic Assessment of the Mitral Valve**

| | |
|---|---|
| Morphology | Mitral annulus, leaflets, chordae, papillary muscles, LV size and function, LA size, pulmonary hypertension (RVSP) |
| Stenosis | Often rheumatic<br>*ECHO score:* Leaflet mobility, thickening, subvalvular thickening, calcifications, <8 favors valvuloplasty<br>*Severe MS:* Area ≤1 $cm^2$ or mean gradient >10 mm Hg |
| Regurgitation | Regurgitant jet size does not correlate well with severity<br>*Severe MR:* Dilated LV (ESD >45 mm), ↓ LV systolic function (EF <55–60%), dilated LA, pulmonary hypertension (RVSP >50) |

EF, ejection fraction; ESD, end-systolic dimension; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; MS, mitral stenosis; RVSP, right ventricular systolic pressure.

***Mitral Valve Prolapse.*** Mitral valve prolapse (MVP) is the most common cause of MR in patients undergoing cardiac surgery in the United States.[19] MVP is the systolic billowing or displacement of at least 2 mm of either mitral leaflet into the LA beyond the plane of the mitral annulus in the parasternal or apical long-axis views (see Fig. 56-7). Recent criteria for echo diagnosis of MVP have become more stringent,[20] leading to increased specificity of the criteria for MVP while at the same time preserving sensitivity for the detection of MVP complications. Classic MVP is defined as equal to or greater than 5 mm of leaflet thickening (myxomatous changes) of the prolapsing leaflet, while nonclassic prolapse is leaflet thickening less than 5 mm. Compared to nonclassic MVP, classic MVP has a worse prognosis, with most complications of MVP (significant MR and congestive heart failure, MV surgery, infectious endocarditis) arising in patients with classic MVP.[19] Asymmetrical prolapse of the leaflets is associated with progression to more significant disease (flail leaflet and severe MR).

Determining which segment of the mitral leaflet tissue is prolapsing is essential for proper MV repair. MR associated with MVP often has an eccentric jet directed opposite to the prolapsing leaflet (e.g., anteriorly directed jet if posterior leaflet prolapse is present). In contrast, in MR associated with rheumatic MS, the regurgitant jet is directed toward the affected leaflet due to restricted leaflet motion (e.g., anteriorly directed jet if the anterior leaflet is calcified). MR associated with MVP may be due to flail leaflet or chordal rupture resulting from myxomatous involvement of the chordae or leaflet. Chordal rupture is diagnosed when the chords are seen as mobile echodensities attached to a flail or partially flail leaflet (Fig. 56-8).[21] Chordal rupture may be difficult to distinguish from vegetations of infective endocarditis. Mitral annulus calcification (MAC) may also be seen in patients who have MVP.

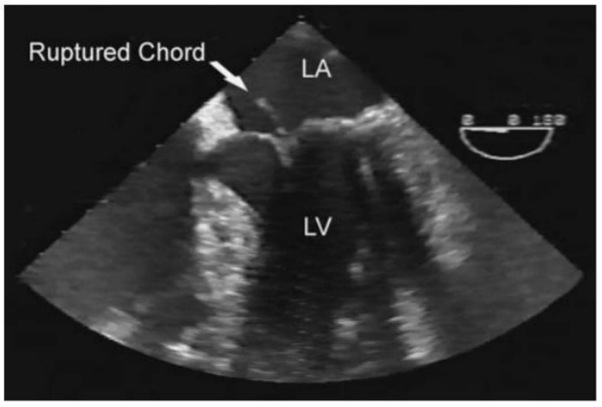



**FIGURE 56-8** Ruptured chord attached to a flail segment of the posterior mitral leaflet due to myxomatous disease. Intraoperative transesophageal echocardiogram showing the ruptured chord as an echodense linear filament attached to the flail leaflet, prolapsing into the left atrium during systole. LA, left atrium; LV, left ventricle.

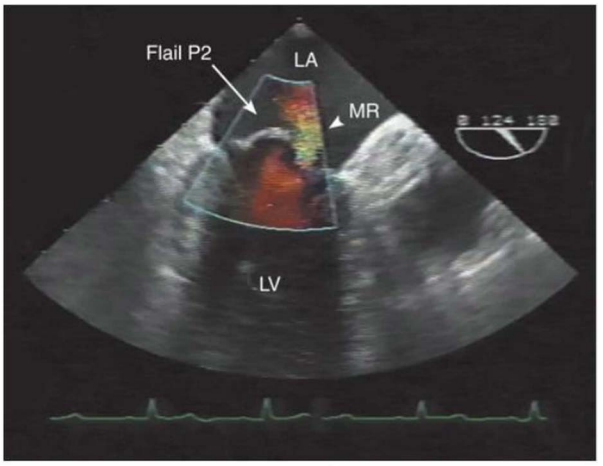



**FIGURE 56-9** Flail mitral leaflet with severe mitral regurgitation. Intraoperative transesophageal echocardiogram with color-flow Doppler consistent with severe mitral regurgitation. This patient underwent successful mitral valve repair with posterior leaflet quadrangular resection and an annuloplasty band. LA, left atrium; LV, left ventricle; MR, mitral regurgitation.

***Flail Leaflet.*** Flail leaflet encompasses a spectrum of disease severity from partially to completely flail leaflets, resulting in excessive motion of the mitral leaflets and various degrees of MR (Fig. 56-9). Flail mitral leaflet is diagnosed when the leaflet tip is "upturned" toward the LA during MV closure (due to loss of coaptation). Most commonly, it is caused by MVP or endocarditis resulting in chordal rupture, but it may also be caused by ischemia or infarction of the papillary muscle. A partially flail leaflet (due to chordal rupture) is usually associated with moderate to severe MR, while a completely flail mitral leaflet is almost always associated with severe MR necessitating surgery.[21]

***Ruptured Papillary Muscle.*** Dysfunction of the papillary muscle results in severe MR and is most often due to acute myocardial infarction. Papillary muscle dysfunction should be differentiated from acute chordal rupture. Papillary muscle rupture is diagnosed in the appropriate clinical context when a triangular mass or balled up mass (the head of the papillary muscle), is seen attached to the anterior or posterior leaflets. The ruptured papillary muscle may prolapse into the LA during systole and in the LV in diastole. Papillary muscle rupture is accompanied by severe MR.[17]

***Leaflet Perforation.*** This is most commonly caused by valvular endocarditis, while less common etiologies include congenital (cleft MV) or iatrogenic causes. With leaflet perforation, the regurgitant jet is often eccentric and originates at the site of perforation.

***Mitral Valve Repair.*** TEE is essential in determining the suitability of a valve for repair. It can assess the mechanism

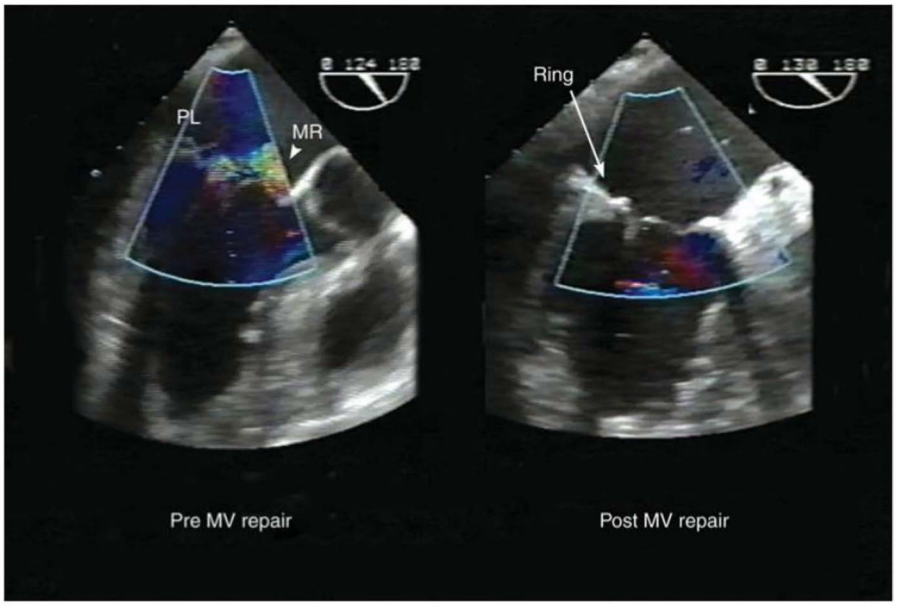



**FIGURE 56-10** Posterior leaflet prolapse and dilated mitral annulus. Note the anteriorly directed eccentric jet of mitral regurgitation seen on transesophageal echocardiography. Following the repair (posterior leaflet quadrangular resection and annuloplasty ring), the patient had good ventricular function and no residual mitral regurgitation. PL, posterior leaflet.

and severity of MR, identify the affected leaflets, determine the presence of coexisting valvular lesions, and estimate RV and LV function. The prognosis of MV repair differs based on the mechanism of MR (organic/primary vs functional/secondary) and is strongly influenced by the preoperative EF. The most common indication for MV repair is myxomatous disease. Determining which leaflet or segment is involved is important in deciding on the suitability of the repair, the likelihood of successful repair (better with posterior leaflet prolapse), and the method of repair. This is done by analyzing the motion of the leaflets and the direction of the regurgitant jet.

TEE is also helpful intraoperatively to assess the success of the repair. Immediately postrepair (Fig. 56-10), the competency of the valve can be assessed for residual MR (1+, mild; 2+, moderate; 3+, moderate to severe; 4+, severe). Phenylephrine and volume may be administered in order to assess the effect of increased afterload and preload on the degree of residual MR. If there is MR postrepair equal to or greater than 2+, further surgery is indicated. Repeat imaging is also done after the patient is off cardiopulmonary bypass. Other findings that may be detected on TEE include residual MS, global or regional LV systolic dysfunction, suture dehiscence or leaflet perforation, and LV outflow obstruction from systolic anterior motion (SAM) of the MV. Limitations to intraoperative TEE include the effect of changing hemodynamics, which may significantly affect the appearance and severity of valvular lesions. Hence, it is important that loading conditions be similar in comparing the severity of MR.

## Aortic Valve

### AORTIC VALVE MORPHOLOGY

Normally, the aortic valve (AV) is composed of three semilunar leaflets (cusps) that open and close passively due to pressure differences between the LV and the aorta. They consist of the right, left, and non coronary cusps. Small strands may be seen on the cusps (Lambl excrescences), particularly on TEE, and represent a normal variant. Bicuspid and rarely unicuspid or quadricuspid valves may be seen on echo (Fig. 56-11). The normal valve area is 3 to 4 $cm^2$ with a 2-cm leaflet separation during systole.

A bicuspid AV is the most common congenital heart defect and occurs in about 1 to 2 percent of the US population. The morphologic features of a bicuspid AV are somewhat variable. The anterior–posterior configuration arises when the right and left coronary cusps are fused and this orientation is seen more commonly. The right–left configuration occurs when the right and noncoronary cusps are fused. In most patients, the two cusps are unequal in size with larger right or anterior leaflets. A well-defined raphe is sometimes present that may give the appearance of a trileaflet valve. In many others, the cusps may be unequal in size with an eccentric commissure, with the larger of the two cusps containing a raphe.[1,22] The M-mode may help in diagnosis in that the closure line of the AV leaflets are eccentric[40]. In the parasternal long-axis views, bicuspid valves are characterized by systolic doming. In the short-axis views, the hallmark is an elliptical "football"-shaped systolic orifice. The valve leaflets themselves may be

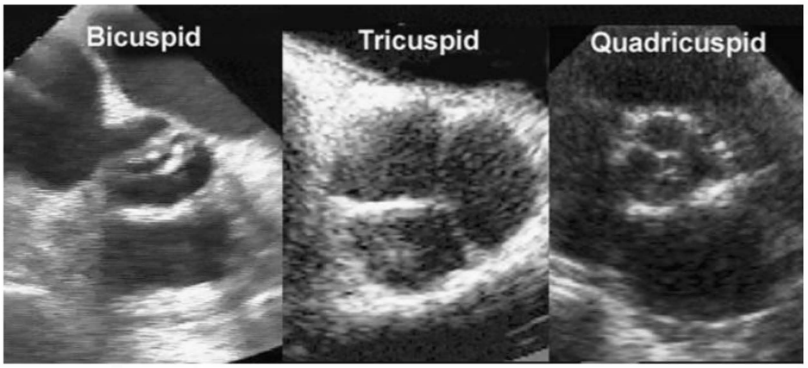



**FIGURE 56-11** Bicuspid, tricuspid, and quadricuspid aortic valves. The normal aortic valve is trileaflet (central panel). Bicuspid valve is the most common congenital anomaly of the aortic valve (left panel), with quadricuspid (right panel) aortic valves being much less common.

thickened and fibrotic, particularly with increasing patient age. A bicuspid valve may be functionally normal with no significant stenosis or regurgitation, particularly in adolescents and young adults, among whom up to one-third have no significant valvular dysfunction.[23] However, over time, fibrosis and valve calcification leads to functional abnormalities. By the age of 60 years, over 50 percent of bicuspid valves are significantly stenotic. Valve regurgitation is frequently present as well and may be the predominant functional abnormality in younger patients. Etiology of the regurgitation may be retraction and fibrosis of the commissures or leaflets, cusp prolapse, dilatation of the aortic root or valve annulus, or damage from infective endocarditis.

It is important to recognize that bicuspid AVs are often associated with abnormalities of the aorta. Concomitant aortic coarctation occurs in a minority. Aortic dissection is another known association, with 5 to 9 percent of patients with dissecting aortic aneurysms having bicuspid valves. Aortic root dilatation may be due to a common developmental defect that affects both the aorta and the valve.[24] Poststenotic dilatation of the ascending aorta can also occur.

## AORTIC STENOSIS

Degenerative calcific disease is the most common cause of aortic stenosis (AS) in the United States. It is often associated with MAC and coronary artery disease. Nodular calcification is often present on the aortic aspect of the valve along the bases of the cusps and may protrude into the sinuses of Valsalva (Fig. 56-12B and C). In contrast to rheumatic AS, there is no commissural fusion in degenerative AS, hence AR is rare. Rheumatic AS (Fig. 56-12A) is usually associated with MV disease. Calcium deposits may be present on both sides of the aortic cusps, resulting in commissural fusion and AR. In younger patients, congenital bicuspid AV accounts for two-thirds of cases of severe AS.[40]

***Two-Dimensional Echocardiography.*** A thorough echo evaluation includes assessing the thickness and calcification of the leaflets, their mobility, looking for the etiology of stenosis (e.g., bicuspid, rheumatic, degenerative calcific) and its extent, the presence of other valvular lesions, and assessing LV size and function. TTE is often superior to TEE in assessing the severity of AS because obtaining maximal velocity jets (i.e., absolutely parallel to flow) is often difficult with TEE.

***Aortic Valve Area.*** In aortic stenotic lesions, the AV area decreases by approximately 0.1 $cm^2$/year, although large variations from patient to patient exist.[25] The AV area is usually determined using the continuity equation. Direct planimetry (visualization of the orifice area) is less reliable for patients with heavily calcified valves (due to shadowing of the valve) and for critical ("pinhole") stenoses.[22] The continuity equation is based on the principle of conservation of flow (or mass), whereby flow before the valve must equal flow across the valve. Since the area of the LV outflow tract (LVOT) can be directly measured, as can velocities in the LVOT and across the valve, the AV area can then be calculated:

$$A_1 V_1 = A_2 V_2$$

where $A$, area or $\pi r^2$; $V$, velocity; $A_1 V_1$ flow proximal to the valve (LVOT); $A_2 V_2$, flow across the valve.

The major limitation to the continuity equation is that small errors in the LVOT diameter become magnified in estimating the AV area (since the radius is squared in the equation). As a general rule, one may assume that the LVOT diameter is 2 cm ($r_1 = 1$ cm) with generally good estimates of the AV area. LVOT is measured in midsystole and the parasternal view provides the most accurate assessment[39]. Another limitation to the continuity equation is in obtaining the maximal aortic jet velocity, which requires that the echocardiographic Doppler beam be exactly parallel to the direction of blood flow.

***Aortic Valve Pressure Gradients.*** Like pressure gradients obtained for MS, the simplified Bernoulli equation is used for estimating AV pressure gradients:

$$\Delta P = 4V^2$$

where $\Delta P$, AV pressure gradient (mm Hg) and $V$, velocity of blood flow across the AV (ms).

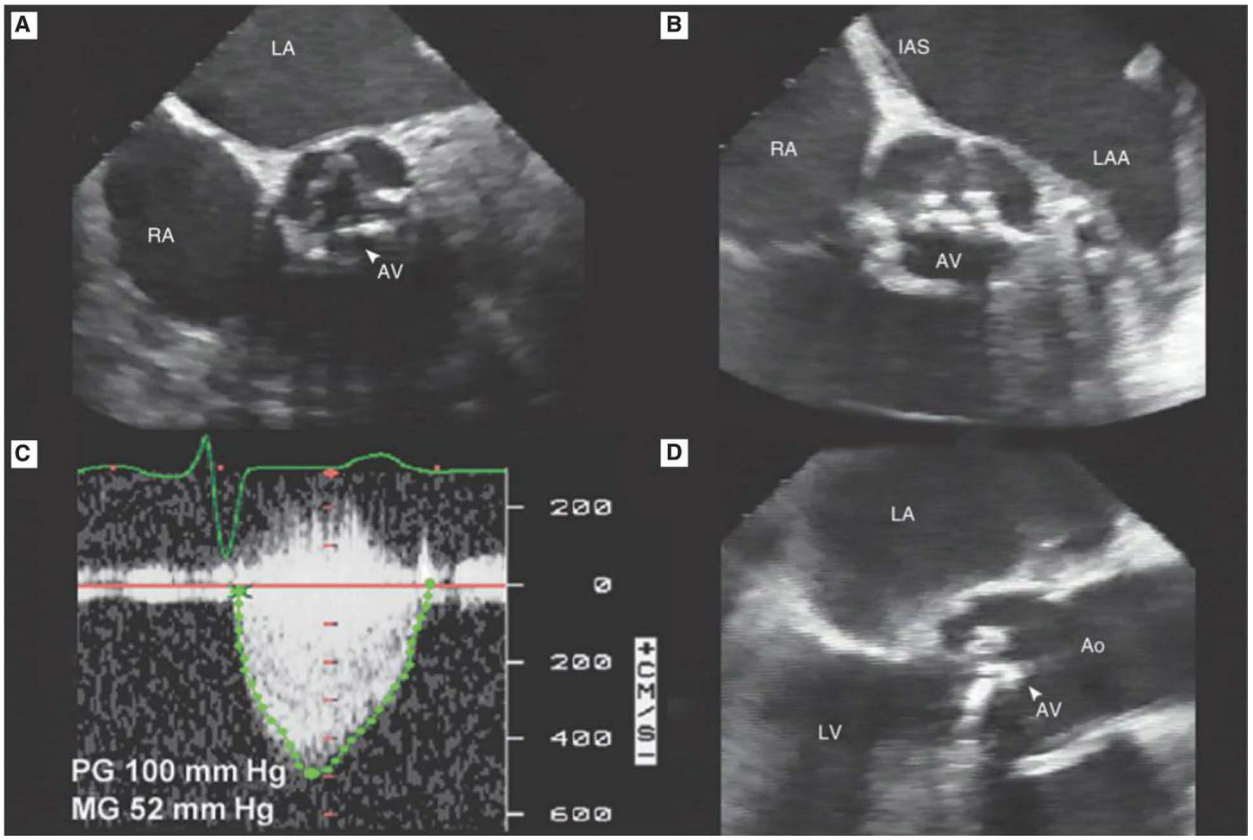



**FIGURE 56-12** Rheumatic and calcific aortic stenosis. **A.** Rheumatic aortic stenosis with calcium deposits in the commissures resulting in commissural fusion. **B** and **D.** Short- and long-axis views: Calcific aortic stenosis, with calcium deposits on the aortic aspect of the valve on the bases of the cusps and no commissural fusion. **C.** Continuous-wave (CW) Doppler of the aortic valve (shown in B and C) is consistent with severe aortic stenosis (aortic velocity >4 ms, mean gradient >50 mm Hg). RA, right atrium; LA, left atrium; AV, aortic valve; LAA, left atrial appendage; IAS, interatrial septum; Ao, aorta; PG, peak gradient; MG, mean gradient.

AV pressure gradients may be significantly underestimated because of inadequate envelopes (because the Doppler beam is not parallel to the blood flow) or an inadequate number of measurements from different locations. Maximal velocities may be present or obtainable from only certain locations in an individual patient. Hence, complete assessment from all images is required. In addition, the velocity of flow is highly dependent on overall LV function. Pressure gradients may significantly underestimate the severity of AS in the presence of severe LV dysfunction ("low-gradient AS"). The opposite is also true, whereby increased flow velocity across the valve is seen in situations of increased cardiac output (i.e., anemia, AR, hyperthyroidism) and may not reflect true AS. In such situations, valve area calculations may be more accurate, and correlation with valve morphology and visual assessment of leaflet mobility is important.

***Severity of Aortic Stenosis.*** The mean AV pressure gradient and the AV area are used to estimate severity of AS and the need for surgical intervention (Table 56-4). If there is a significant discrepancy between the pre- and intraoperative grading of the severity of AS, the following should be considered:

1. Change in hemodynamic conditions: Changes in heart rate or rhythm, contractility, and hemodynamics influence the gradients across the AV. The AV area is usually less affected by loading conditions. The pressure gradient will rise with an increase in stroke volume such as exercise and coexisting AR and decrease with sedation and hypovolemia when stroke volume decreases.[39]
2. Measurement variability in data recording: Measurement errors in the LVOT diameter lead to large errors in calculating the AV area, since the LVOT radius is squared in the continuity equation.

## AORTIC REGURGITATION

AR can result either from valve pathology or from conditions that affect the aortic root. Echo assessment of AR includes a

**TABLE 56-4: Severity of Aortic Stenosis**

| Severity | Velocity (m/s) | Area ($cm^2$) | Mean Gradient[a] (mm Hg) |
|---|---|---|---|
| None | 1 | 3–4 | – |
| Mild | 2.5–2.9 | >1.5 | <25 |
| Moderate | 3–4 | 1–1.5 | 25–50 |
| Severe | >4 | <1 | >50 |

[a]Assumes normal cardiac output.

Reproduced from: ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease. A report of the American College of Cardiology/American Heart Association. Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *J Am Coll Cardiol* 1998;32:1486–1588. Copyright Elsevier.

comprehensive examination of AV morphology, aortic root dimensions, and LV size and function.[16] TTE is generally the initial diagnostic test used for evaluating the severity of AR. However, TEE is also helpful particularly for patients with poor transthoracic windows, if prosthetic valves are present, and intraoperatively to guide surgical repair. TEE is particularly useful for determining the mechanism of regurgitation by distinguishing valvular from nonvalvular causes of AR. Common etiologies for AR include those that cause AS with subsequent AR. Common causes include congenital malformations (bicuspid valves); degenerative calcific, myxomatous, rheumatic, and infective endocarditis; aortic aneurysm (Fig. 56-13) or dissection; Marfan syndrome; drug-induced AR; and prosthetic valve dysfunction.[9] Common etiologies for aortic root dilation include hypertension, aortic dissection, cystic medical necrosis, Marfan syndrome, bicuspid AV, and autoimmune diseases.

Acute and chronic AR differ in both their pathophysiology and echo findings. Many of the echo findings in chronic AR (e.g., LV dilatation and systolic dysfunction) may not be present in acute AR. Chronic AR is a state of both pressure and volume overload of the LV, resulting in LV hypertrophy and dilatation and increased chamber sphericity. Initially LV end-diastolic pressure is preserved, but over time, EF declines

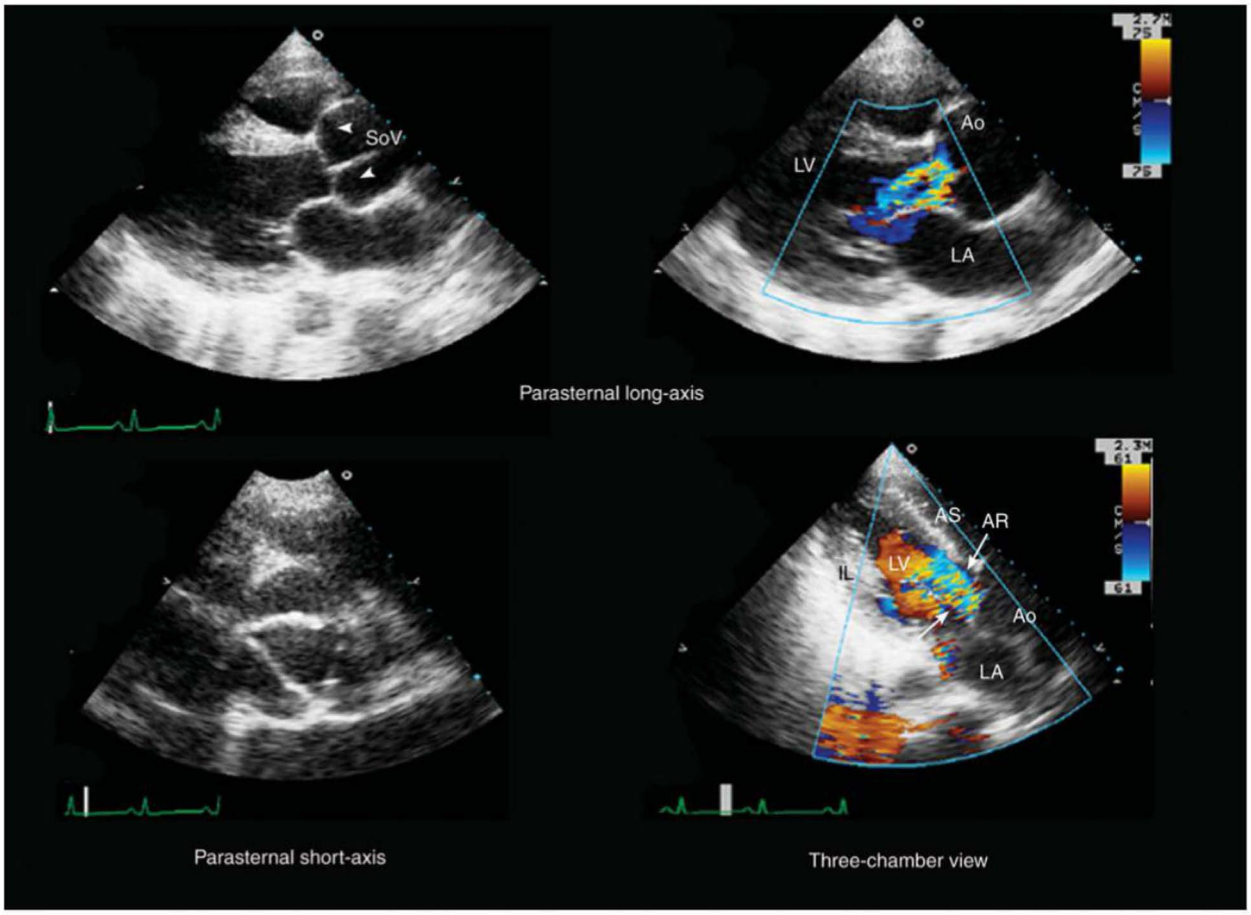



**FIGURE 56-13** Aortic aneurysm of the sinuses of Valsalva and secondary aortic regurgitation. The aortic wall is thin at the sinuses of Valsalva and aneurysmal dilatation results in aortic regurgitation. Note the wide base of the regurgitant jet (vena contracta) consistent with severe aortic regurgitation (arrow). Ao, aorta; AR, aortic regurgitation; LA, left atrium; LV, left ventricle; SoV, sinuses of Valsalva.

due to chronic volume overload and decreased compliance. Acute AR is characterized by normal LV size, elevated EDP, and steep CW Doppler slope.

***Two-Dimensional Echocardiography.*** This is helpful for evaluating LV size and function, AV structure and leaflet mobility, aortic root dilatation, aortic dissection, associated vegetations, diastolic fluttering motion of MV leaflets, and premature MV closure (indicative of significant AR).

***Severity of Aortic Regurgitation.*** In assessing the severity of chronic AR, it is essential to combine data on LV size and function with Doppler data and not to rely solely on color Doppler, since it is often misleading. No study has yet demonstrated that quantification of the severity of AR by Doppler criteria alone is predictive of outcome. Instead, LV size and function are used for risk stratification of asymptomatic patients with chronic AR. Echo findings in severe AR include:

- Dilated LV: minor-axis dimension >50 to 55 mm in systole or >70 to 75 mm in diastole
- LV EF <55 percent
- PHT <200 ms
- Proximal regurgitant color jet width/LVOT diameter ≥65 percent
- Vena contracta >6 mm
- Holodiastolic flow reversal in the thoracic aorta (100 percent sensitive and 97 percent specific for severe AR).
- Restrictive filling pattern to the MV inflow

In comparison to men, women with AR should be considered for surgery before severe symptoms have developed and for smaller LV dimensions. In a recent study, intraoperative mortality was similar for men and women, but 10-year survival was significantly worse for women than for men (39 vs 72 percent, respectively).[26]

In acute AR, many of the features of chronic volume overload will not be present. The severity will be need to be assessed by evaluation of CF Doppler jet width, presence of significant pulmonary hypertension, and evidence by Doppler of rapid equilibration of aortic and LV diastolic pressure (short diastolic half-time <200 ms, short mitral deceleration time <150 ms, or premature closure of the MV). Echo assessment of the AV is summarized in Table 56-5.

**TABLE 56-5: Echocardiographic Assessment of the Aortic Valve**

| | |
|---|---|
| Morphology | Three semilunar leaflets/cusps, LV size and function |
| Stenosis | Often degenerative/calcific<br>*Severe AS:* Area <1 $cm^2$ or mean gradient >50 mm Hg |
| Regurgitation | Regurgitant jet size does not correlate well with severity<br>*Severe AR:* Dilated LV (ESD >50–55 mm), LVH, ↓ LV systolic function (EF <55%)<br>*Acute AR:* LV dilatation/systolic dysfunction may be absent |

AR, aortic regurgitation; AS, aortic stenosis; ESD, end-systolic dimension; LV, left ventricle; LVH, left ventricular hypertrophy.

## Tricuspid Valve

### TRICUSPID VALVE MORPHOLOGY

Normal function of the TV depends on the normal function of its components: annulus, leaflets, chordae, papillary muscles, right atrium, and ventricle.

### TRICUSPID STENOSIS

Tricuspid stenosis (TS) is not common in adults. The most common cause of TS is rheumatic, which results in both stenosis and regurgitation of the TV and is often associated with concomitant mitral or AV disease. Carcinoid heart disease tends to involve the valves on the right side of the heart as well. Echo assessment of TS is similar to that of MS. The valve leaflets are thickened and shortened. The mean gradient across the TV is normally <2 mm Hg. TS is considered severe when the mean gradient is ≥7 mm Hg and the PHT is ≥190 ms.

### TRICUSPID REGURGITATION

As in the case of the AV and MV, TTE or TEE evaluation of TR focuses on the identification of the etiology or mechanism of TR as well as its hemodynamic severity. TR is the most common abnormality of the TV. Mild TR is a normal finding in 90 percent of individuals (38). Pathologic TR is often secondary to RV dysfunction, RV dilatation causing annular dilation, or significant systolic pulmonary hypertension (systolic pulmonary artery pressures >55 mm Hg). Primary causes of TR are less common (Ebstein anomaly, endocarditis, trauma, anorectic drugs, carcinoid, myxomatous or rheumatic valvular disease, radiation). The tricuspid valve is affected in 20 to 30 percent of patients with rheumatic disease and usually occurs with concomitant mitral or AV involvement.

Patients with severe TR of any cause have poor long-term outcomes because of RV dysfunction and/or systemic venous congestion. TV reconstruction, annuloplasty, or valve replacement is indicated in some cases of severe TR.

TEE is useful intraoperatively to assess the need for TV surgery when TR is secondary to annular dilatation and/or elevated pulmonary artery pressures, particularly during MV surgery. After correction of MV disease, TV surgery may be required if persistent severe TR or annular dilatation (≥30 mm) is still present (Fig. 56-14).[27]

***Severity of Tricuspid Regurgitation.*** Using color Doppler, mild TR is characterized by a jet area in the right atrium of <5 $cm^2$, moderate regurgitation has a jet area of 5 to 10 $cm^2$ of the RA, and severe TR has a jet area of >10 $cm^2$.

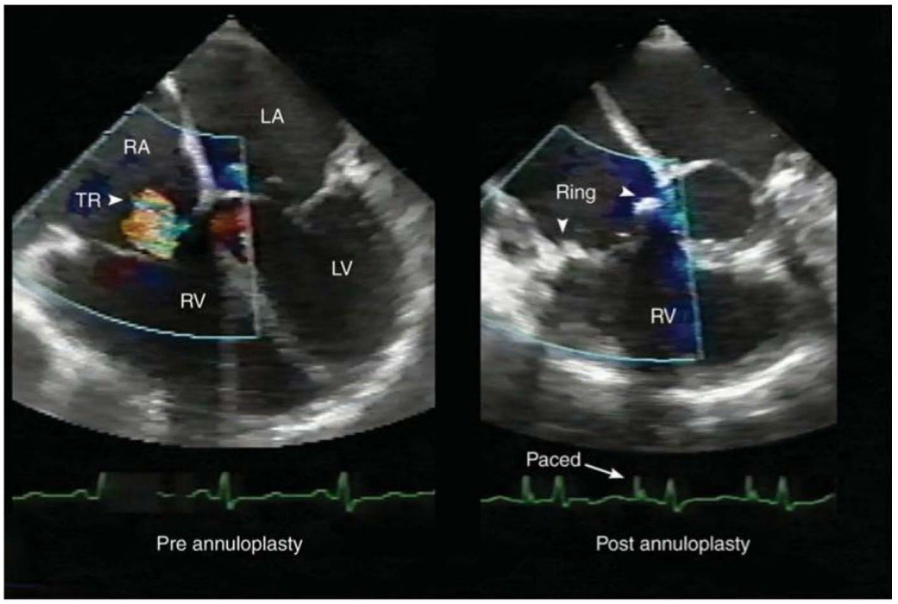



**FIGURE 56-14** Tricuspid valve annuloplasty. This patient had infective endocarditis r esulting in flail posterior mitral valve leaflet and tricuspid regurgitation. He underwent mitral valve repair and tricuspid valve annuloplasty. Note the dilated atria and tricuspid annulus preprocedure and the pacer spikes on the rhythm strip postprocedure. RA, right atrium; TR, tricuspid regurgitation; RV, right ventricle; LA, left atrium; LV, left ventricle.

Echo findings in severe TR include the following[16]:

- A large regurgitant (color) jet (area >10 $cm^2$), vena contracta >7 mm, or eccentric jet. Vena contracta is the most accurate approach; when >7 mm it is 89 percent sensitive and 93 percent specific for severe TR.
- Annular dilatation (≥30 mm), leaflet coaptation, anatomic clues (e.g., vegetations, myxomatous disease)
- Dilated right atrial (RA)
- Dilated RV and paradoxical interventricular septal wall motion
- Pulmonary hypertension
- Dilated venae cavae and hepatic veins with minimal respiratory flow variation and systolic flow reversal

**Estimation of Right Atrial Pressure**

| IVC Diameter | Change with Respiration or Sniff | Estimated RA Pressure |
|---|---|---|
| Small (<1.2 cm) | Spontaneous collapse | Volume depletion |
| Normal (<1.7 cm) | Decrease by ≥50% | 0–5 mm Hg |
| Dilated (>1.7 cm) | Decrease by ≥50% | 5–10 mm Hg |
| Dilated (>1.7 cm) | Decrease by <50% | 10–15 mm Hg |
| Dilated (>1.7 cm) | No change | 15–20 mm Hg |
| Dilated with dilated hepatic vein | No change | >20 mm Hg |

Data from Kircher BH, Himelmann RB, Schiller NJ. *Am J Cardiol* 1990;66:493, and from Lang RM, Bierig M, Devereux RB, et al. *J Am Soc Echocardiog* 2005;18:1440.

### PULMONARY HYPERTENSION

The velocity of the tricuspid regurgitant jet is an accurate measure used to estimate the pulmonary artery systolic pressure. In the absence of pulmonary stenosis, pulmonary artery systolic pressure is equal to RVSP. RVSP is estimated using the simplified Bernoulli equation ($\Delta P = 4V^2$) from the peak TR velocity ($V$). $\Delta P$ is then the pressure gradient across the TV, or the pressure difference between the RA and RV ($\Delta P = P_{RV} - P_{RA}$). In the absence of elevated RA pressures, the RA pressure ($P_{RA}$) is estimated at 10 mm Hg. Therefore,

$$RVSP = P_{RA} + \Delta P = 10 + 4V^2$$

where RVSP, RV systolic pressure and $V$, peak TR velocity (ms).

RA pressure can be estimated by respiratory variation in the IVC. This is best assessed in the subcostal view.

***Severity of Pulmonary Hypertension.*** Normal pulmonary artery systolic values are 18 to 25 mm Hg with a mean of 12 to 16 mm Hg.[2] Pulmonary hypertension is defined as systolic pulmonary artery pressure greater than 30 mm Hg or mean pulmonary artery pressure less than 20 mm Hg at rest.[2] Commonly used values using RVSP to estimate the severity of pulmonary hypertension are shown in Table 56-6.

## Prosthetic Valves

Any evaluation of prosthetic valve function should include an assessment of transvalvular pressure gradients and valve area, similar to the evaluation of native valve function.

**TABLE 56-6: Severity of Pulmonary Hypertension**

| | RVSP (mm Hg) |
|---|---|
| Normal | 18–25 |
| Mild | 30–40 |
| Moderate | 40–70 |
| Severe | >70 |

RVSP, right ventricular systolic pressure.

Structural or mechanical failure is usually a disease process unique to prosthetic valves causing failure of the device to open or close properly. This usually occurs over a period of time and can involve tissue degeneration or fibrocalcific changes of the valve leaflets. Acute stenosis is rare but may be caused by acute valve thrombosis. Prosthetic valves can also develop paravalvular leaks, chronic thrombus, or pannus formation as well as endocarditis.[39] TTE is helpful in the initial assessment of prosthetic valve dysfunction. However, its sensitivity is impaired by difficulty in visualizing structures around and behind the prosthesis, particularly for mechanical valves. Prosthetic material attenuates the ultrasound beam and causes multiple reverberations and acoustic shadowing, thus hampering interpretation. TEE is often required for the complete evaluation of prosthetic valve structure and function. Cinefluoroscopy may also be a relatively quick and useful method for determining leaflet mobility in mechanical valves and is indicated when mechanical valve thrombosis is suspected. When valve dysfunction is suspected, 2D echo with Doppler and color flow in addition to TEE may be necessary for a comprehensive evaluation of valve function. Such an evaluation of valve function is summarized in Table 56-7.[28] TEE findings in common complications of prosthetic valves are shown in Table 56-8.[28]

**TABLE 56-7: Evaluation of Prosthetic Valves**

| | |
|---|---|
| Pressure gradients | $\Delta P = 4V^2$ |
| Valve area | *MV prostheses:* Area = 220/PHT<br>*AV or MV prostheses:* $A_1V_1 = A_2V_2$ |
| Regurgitation/leaks | Size, symmetry, velocity, eccentricity |
| Leaflet mobility/restriction | Degree of leaflet excursion |
| LV size/function | LV dimensions, EF |
| Pulmonary hypertension | RVSP = $4V^2 + 10$ |
| Compare with prior ECHO | Change in gradients, area, leaks |

$\Delta P$, pressure gradient; $V$, velocity; MV, mitral valve; AV, aortic valve; $A_1V_1$, flow (area$_1$ × velocity$_1$) proximal to the valve prosthesis; $A_2V_2$, flow (area$_2$ × velocity$_2$) across the valve prosthesis; RVSP, right ventricular systolic pressure.

Data from Zabalgoitia M. Echocardiographic recognition and quantitation of prosthetic valve dysfunction. In: Otto CM (ed). *The Practice of Clinical Echocardiography*. Philadelphia: Saunders, 2002:525–550. With permission. Copyright Elsevier.

**TABLE 56-8: TEE Findings in Prosthetic Valve Complications**

| | |
|---|---|
| Paravalvular leak | Large, wide eccentric jet with high velocity, turbulent flow |
| Structural deterioration | Dehiscence, regurgitation, stenosis<br>Calcific degeneration (bioprostheses) |
| Nonstructural dysfunction | Often due to inappropriate sizing<br>Stenosis or regurgitation |
| Thrombosis | Decreased range of motion or maximum excursion<br>Stenosis (± regurgitation)<br>Distinguish from fibrin strands which are small filaments on atrial aspect of mitral or ventricular aspect of aortic valves |
| Pannus formation | Stenosis |
| Infective endocarditis | Irregular echogenic mobile mass or masses on valve<br>Regurgitation (± stenosis)<br>Leaflet destruction (bioprostheses)<br>Perivalvular abscess (valve rocking, periaortic root thickening, echolucency)<br>Perivalvular dehiscence, fistula tract |

Data from Zabalgoitia M. Echocardiographic recognition and quantitation of prosthetic valve dysfunction. In: Otto CM (ed). *The Practice of Clinical Echocardiography*. Philadelphia: Saunders, 2002:525–550. With permission. Copyright Elsevier.

## PROSTHETIC VALVE PRESSURE GRADIENTS

Like native valve gradients, prosthetic valve pressure gradients can be obtained using the simplified Bernoulli equation ($\Delta P = 4V^2$). Compared to normal native valves, homografts and the newer nonstented bioprostheses have similar velocities and pressure gradients, while mechanical valves have higher flow velocities. Prosthetic valves except ball–cage valves normally have pressure gradients since they are by design obstructive, with gradients increasing as valve size decreases. High gradients are often seen with 19-mm AV prostheses. High gradients in prosthetic valves may be seen for other reasons as well, such as high cardiac output, valve obstruction, or significant valvular regurgitation (due to increased flow).

## PROSTHETIC VALVE AREA

As in the case of native valves, prosthetic valve area can be calculated using the continuity equation or PHT method. For AV prostheses, the continuity equation ($A_1V_1 = A_2V_2$) is usually used. The LVOT diameter or outer diameter of the sewing ring (not its internal diameter) should be measured for accurate estimation of $A_1$. For MV prostheses, use of the continuity equation is preferred, since the PHT equation may overestimate the true prosthetic MV area. The continuity equation should not be used if there is significant AR or MR. The same equations may be used for the calculation of prosthetic TV areas.

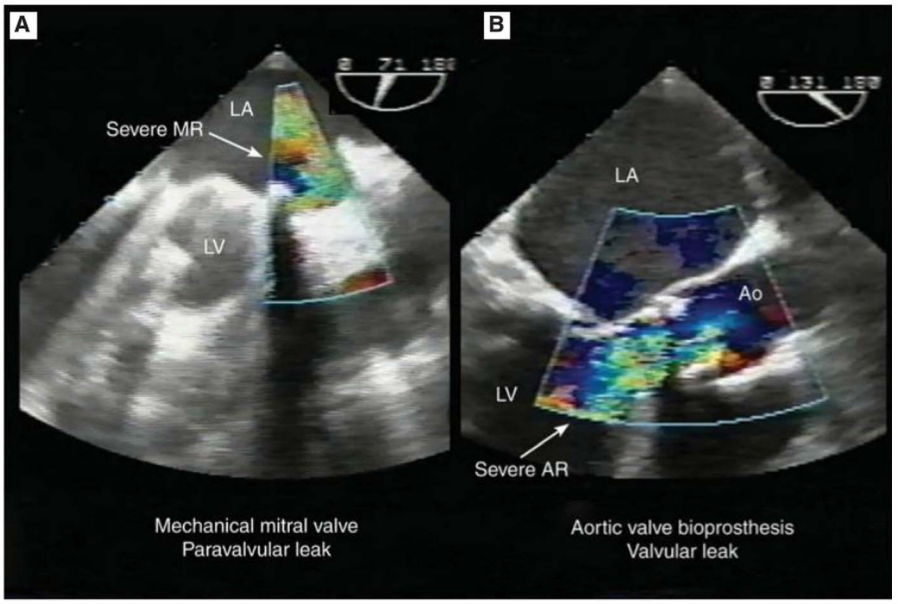



**FIGURE 56-15** Paravalvular and valvular leaks. **A.** Bileaflet mechanical mitral prosthesis with severe paravalvular regurgitation secondary to endocarditis and partial valve dehiscence, requiring valve replacement. **B.** Aortic bioprosthesis with severe aortic regurgitation due to calcific degeneration and a torn leaflet. LA, left atrium; LV, left ventricle; MR, mitral regurgitation; Ao, aorta.

### PARAVALVULAR LEAKS

Normal amounts of regurgitation are expected with prosthetic valves owing to the built-in transvalvular regurgitation ("closing volume"). The amount of regurgitation increases with valve size, the size of the gap between the occluder and the rim, and lower heart rates. Echo findings[4] of normal prosthetic valve regurgitation include:

1. AV: regurgitant area <1 $cm^2$ and length of jet 1.5 cm
2. MV: regurgitant area <2 $cm^2$ and length of jet 2.5 cm
3. Characteristic flow patterns (Medtronic-Hall, one central jet; Star–Edwards, two curved side jets; Bjork–Shiley, two unequal side jets; St. Jude Medical, two side jets and one central jet)

Larger leaks in other locations (Fig. 56-15) are abnormal and may be associated with significant hemodynamic compromise, hemolysis, or valve dehiscence.[28] TEE is often required to fully assess prosthetic valve regurgitation because of the limited sensitivity of TTE. Echo characteristics that differentiate physiologic from nonphysiologic regurgitation are summarized in Table 56-9.[28]

## INFECTIVE ENDOCARDITIS

TEE is the procedure of choice for the detection of vegetations in infective endocarditis, with better sensitivity (50 percent for TTE vs 90 percent for TEE) and specificity (95 percent for TTE vs >95 percent for TEE) for native valve endocarditis compared to TTE.[29,30] Characteristics of valvular vegetations are listed in Table 56-10.[29] However, early in the course of infective endocarditis, vegetations may not have these typical characteristics and TEE should be repeated if the clinical suspicion is high. It may be difficult to identify a vegetation involving a native valve that is calcified or structurally abnormal. Compared with native valve endocarditis, it is more difficult to identify vegetations on prosthetic valves because of artifact from the prosthetic materials. Often both TTE and TEE are useful to detect vegetations, although TTE has lower sensitivity compared with TEE for prosthetic valve endocarditis.[8] TEE is particularly sensitive for identifying ring abscesses.

AV vegetations usually develop on the ventricular side of the leaflet. They exhibit rapid independent motion and may prolapse into the LVOT during diastole. Rapid oscillating

**TABLE 56-9: Physiologic and Nonphysiologic Valvular Regurgitation**

| Regurgitant Jet | Physiologic | Nonphysiologic |
|---|---|---|
| Size | Small, narrow | Large, wide |
| Symmetric | Yes | No |
| Velocity | Low | High |
| Eccentric | No | Yes |

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**TABLE 56-10: Echocardiographic Characteristics of Vegetative and Nonvegetative Valvular Masses**

| Characteristic | Vegetation | Not Vegetation |
|---|---|---|
| Echogenicity | Similar to myocardium<br>Low echogenicity/gray | Similar to pericardium<br>High echogenicity/white |
| Location | Upstream surface of valve near the regurgitant jet | Downstream surface of valve |
| Motion | Mobile, prolapses | Less mobile |
| Shape | Amorphous, lobulated wide base of attachment<br>Severe regurgitant jet | Filamentous, strand-like narrow base of attachment<br>Mild or no regurgitant jet |
| Regurgitation | Vegetation located near jet | |
| Other | Paravalvular abscess/leak<br>Fistula<br>Valve dehiscence | None |

Data from Schiller NB. Clinical decision making in endocarditis. In: Otto CM (ed). *The Practice of Clinical Echocardiography*. Philadelphia: Saunders, 2002:451–468. With permission. Copyright Elsevier.

motion is also seen on M-mode imaging. MV vegetations typically occur on the atrial side of the leaflets. They also exhibit rapid independent motion and may prolapse in the LA during systole[39].

It is important to differentiate infective vegetations from other intracardiac masses, which include papillary fibroelastoma, nonbacterial thrombotic endocarditis, thrombus, Lambl excrescence or nodule of Arantis, and myxomatous valve disease. Lambl excrescences are thin, strand-like fibroelastic projections. The incidence of these masses increases with advancing age.

Complications of infective endocarditis (Fig. 56-16) include the following:

1. Paravalvular abscesses
2. Valve destruction or perforation, leaflet rupture, or dehiscence of prosthetic valves
3. Fistulas
4. Pseudoaneurysms
5. Emboli

## EVALUATION OF SPECIFIC DISORDERS

### Coronary Artery Disease

#### MYOCARDIAL ISCHEMIA/INFARCTION

The echo manifestation of myocardial ischemia is a decrease in contractility or systolic wall thickening of the ischemic territory that is manifest within seconds of the onset of ischemia, prior to evidence of electrocardiographic ischemia.[4] Decreased or absent wall thickening

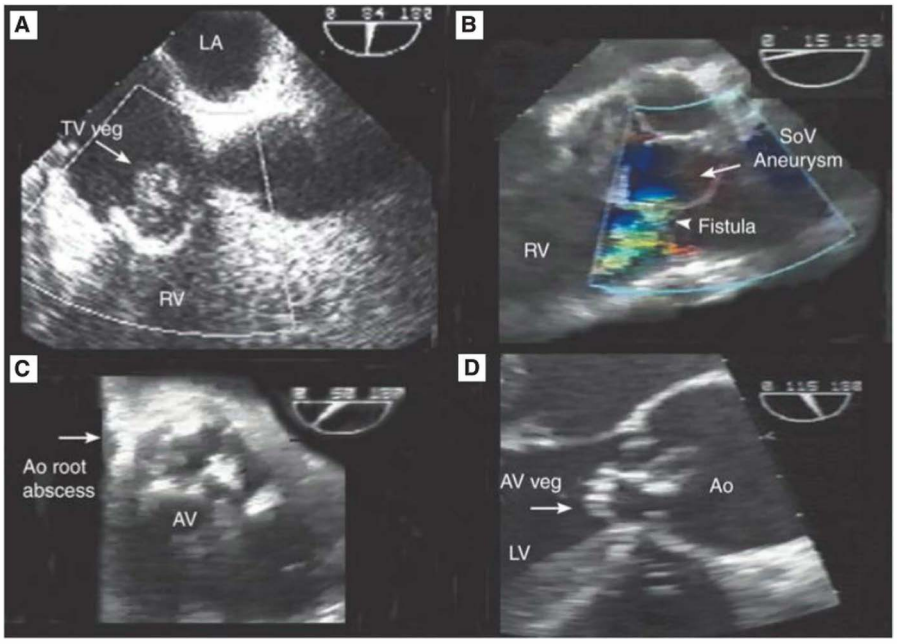



**FIGURE 56-16** Complications of infective endocarditis. **A.** Large vegetation on bioprosthetic tricuspid valve seen on transesophageal echocardiogram. **B.** Sinus of Valsalva aneurysm and aortic–right ventricular fistula. **C.** Bicuspid aortic valve with bacterial endocarditis complicated by large aortic root (annular) abscess (note the thickened perivalvular tissue) and complete heart block requiring emergent surgery. **D.** Large aortic valve vegetation prolapsing into the left ventricular outflow tract during systole. Ao, aorta; AV, aortic valve; LA, left atrium; LV, left ventricle; RV, right ventricle; SoV, sinus of Valsalva; TV, tricuspid valve.

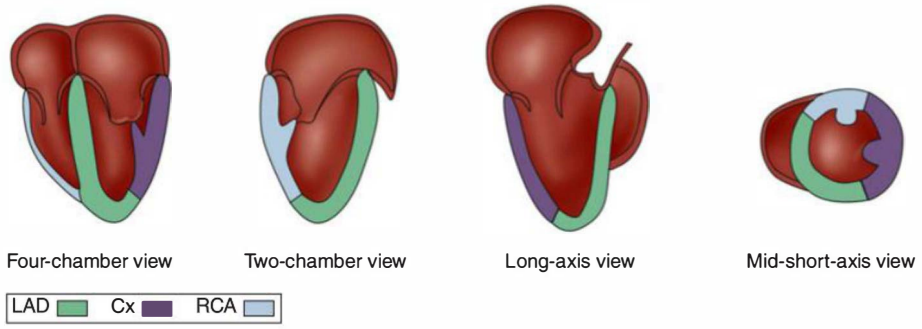



**FIGURE 56-17** Common myocardial perfusion patterns by each of the three major coronary arteries. LAD, left anterior descending; Cx, left circumflex; RCA, right coronary artery. (From Shanewise JS, Cheung AT, Aronson S, et al. ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: Recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography. *J Am Soc Echocardiogr* 1999;12:884–900. With permission. Copyright Elsevier.)

is a better indicator of ischemia than wall motion, since infarcted myocardium may be passively pulled or tethered by adjacent normal myocardium, resulting in apparent wall motion without active contraction. Ancillary signs of ischemia include an increase in end-systolic LV volume and a decrease in global contractility or EF.[4] Hypokinesis is decreased contractility (<30 percent wall thickening); akinesis is the absence of contractility (<10 percent wall thickening); and dyskinesis is outward motion during systole. Echo is accurate at localizing the site of coronary obstruction (Fig. 56-17). However, it usually overestimates infarct size due to myocardial stunning, which has resulted in a lack of correlation between wall motion abnormalities detected on echo in the setting of an acute myocardial infarction and infarct extent.[31]

## ISCHEMIC, INFARCTED, STUNNED, OR HIBERNATING MYOCARDIUM?

Myocardial segments may be dysfunctional secondary to ischemia, infarction/scar, or stunned or hibernating myocardium. Stunned myocardium is postischemic ventricular dysfunction that occurs when reperfusion of the occluded artery has been achieved but the wall motion and thickening of the corresponding myocardial segment remain abnormal—a condition that may last for days to weeks. Hibernating myocardium results from chronic ischemic dysfunction when the myocardial tissue is chronically hypoperfused owing to inadequate blood flow, resulting in abnormal wall motion and thickening, but it usually recovers after successful revascularization. Resting echo may help differentiate viable (stunned or hibernating) myocardium from nonviable (infarcted or scarred) myocardium based on wall thickness. Thicker myocardium is more likely to be viable, while thinned and fibrotic myocardium most likely represents scar.[4] The specificity of these criteria is quite low; however, viability assessment can be significantly improved with dobutamine or stress echocardiography.[8] A biphasic response on dobutamine echo is the most sensitive parameter for viable myocardium and is associated with improved survival after revascularization. This is evidenced by an improvement in wall motion and thickening or recruitment at low-dose dobutamine (10 to 20 μg/kg/min) followed by worsening of wall motion and thickening at higher doses (30 to 40 μg/kg/min) when the ischemic threshold is reached.

## LEFT VENTRICULAR ANEURYSM AND MURAL THROMBUS

A true ventricular aneurysm consists of a thin myocardial wall (<7 mm) that is echogenic (and sometimes calcified) and has outward motion in both systole and diastole.[31] Most aneurysms occur apically, with inferobasal aneurysms being the second most common. Aneurysms are complications of adverse remodeling following transmural myocardial infarcts. Spontaneous echo contrast (SEC) or mural thrombus may be present within an LV aneurysm and is associated with an increased risk of embolic events. The appearance of an acute mural thrombus (same echogenicity as myocardium) generally differs from that of a chronic thrombus, which tends to be layered with areas of calcification.[31] Compared to TTE, TEE may be limited in detecting apical thrombi because of the often suboptimal visualization of the true LV apex with TEE.

LV pseudoaneurysms can also be complications of acute myocardial infarction and are characterized by the lack of a true myocardial wall. They result from contained free wall myocardial rupture in which a portion of the pericardial space limits frank rupture. Pseudoaneurysms can generally be differentiated from true aneurysms by the presence of a narrow neck (less than half of the maximum diameter) compared to the wider base of a true aneurysm.[31] Flow can be occasionally seen in and out of the pseudoaneurysm.

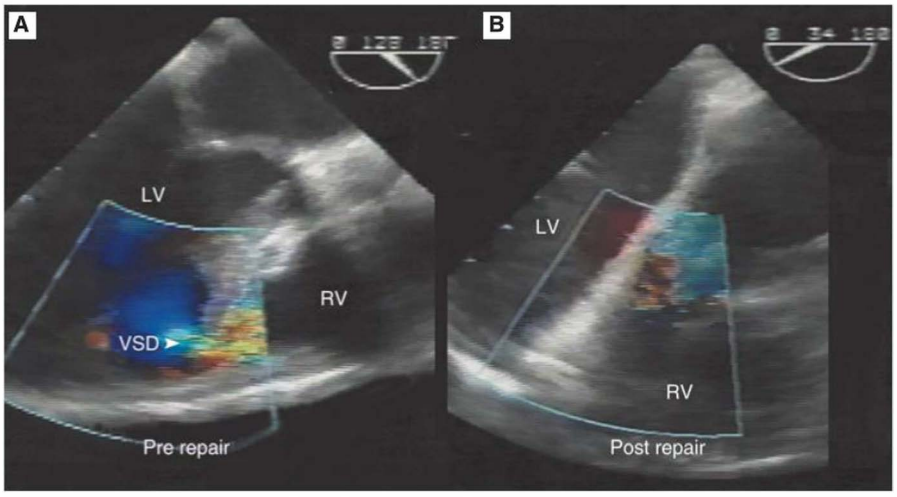



**FIGURE 56-18** Postinfarct ventricular septal defect (VSD). This patient had suffered an acute anterior myocardial infarction that was treated with thrombolytics but subsequently developed a high septal VSD. **A.** Intraoperative transesophageal echocardiogram with color-flow Doppler diagnostic of VSD with high-velocity turbulent flow across the septum. **B.** Surgical repair with a pericardial patch and coronary artery bypass grafting to the ostial left anterior descending artery was successful. Color-flow Doppler shows no flow across the septum. LV, left ventricle; RV, right ventricle.

### POSTINFARCT VENTRICULAR SEPTAL DEFECT

Life-threatening mechanical complications after acute myocardial infarction include free wall rupture, papillary muscle dysfunction/rupture, and ventricular septal defect (VSD) (Fig. 56-18). TTE is usually sufficient for the diagnosis of mechanical complications, although TEE may be used as an adjunct. Postinfarct VSD is uncommon (less than 1 percent of total infarcts), although it is associated with the worst outcome of mechanical complications in patients with cardiogenic shock. Unlike postinfarct papillary muscle rupture, VSD occurs with approximately equal frequency after anterior and inferior infarcts. The posteroapical septum is the most common site to undergo necrosis and rupture. TTE using CF Doppler has a sensitivity of 85 to 95 percent, while TEE has a sensitivity and specificity of 100 percent.[31] A high-velocity left-to-right systolic jet is seen on CW Doppler. Echo characteristics of postinfarct VSD, in addition to the septal defect, include the presence of a small pericardial effusion (PE) with possible intrapericardial thrombus (echogenic mobile mass in the pericardial space) and echo evidence of tamponade.[31]

## THORACIC AORTIC ANEURYSM AND DISSECTION

TTE may diagnose aortic dissection by detecting an intimal flap in the aorta (specificity 95 percent), but it has low sensitivity (80 percent) for ascending aortic dissection and even lower sensitivity for distal thoracic aortic dissection (70 percent).[32] TEE is one of three imaging modalities used for the diagnosis of acute aortic dissection—TEE, computed tomography (CT), and magnetic resonance imaging (MRI)[33,34]—and for the diagnosis of perioperative aortic dissections (Table 56-11). The choice of imaging modality depends primarily on the availability of the imaging procedure and patient characteristics (e.g., hemodynamic instability, presence of a pacemaker, or contrast allergy), since the overall diagnostic accuracy for TEE, CT, and MRI is comparable.[32] TEE is the imaging procedure of choice for patients who are hemodynamically unstable. Compared to CT or MRI, one limitation of TEE is that it cannot image the aortic segment located between the distal ascending aorta and the proximal arch, which may decrease its sensitivity for detection of aortic dissection, hematoma, or atheroma in this region.

The main criterion for TEE diagnosis of suspected acute aortic dissection is the presence of two lumina (false and true) separated by an intimal flap (Table 56-12 and Fig. 56-19). Other findings for diagnosing aortic dissection by TEE[32] include the following:

1. Tear or disruption of the flap continuity or jets seen with color Doppler across the flap
2. Complete obstruction of the false lumen; presence of thrombus
3. Central displacement of intimal calcification or separation of intimal layers from thrombus
4. Periaortic hematoma (echo-free spaces around the aorta)
5. Intramural hematoma (crescent-shaped echodensity with vacuolization within it on the aortic short-axis view)
6. Pericardial or pleural effusion
7. AR

**TABLE 56-11: Diagnostic Tests for Acute Aortic Dissection**

| Test | Sensitivity (%) | Specificity (%) | Advantages and Disadvantages |
|---|---|---|---|
| TEE | 99–100 | >89 | *Advantage*: Quick, semi-invasive, assess AR, coronaries, pericardial effusion, may assess IH.<br>*Disadvantage*: Limited assessment of IH, "blind spot" of distal ascending aorta and anterior aortic arch, reverberation artifact |
| CT | >90 | >85 | *Advantage*: Quick, noninvasive<br>*Disadvantage*: Cannot assess branch vessels or IH, dye load/allergy |
| MRI | 98–100 | 100 | *Advantage*: Noninvasive, assess branch vessels, IH<br>*Disadvantage*: Slow, may not be available, pacemakers/device, breath-hold necessary |
| Angiography | 88–91 | >95 | *Advantage*: Assess coronaries, AR, branch vessels<br>*Disadvantage*: Slow, invasive, dye load, may miss dissection if completely thrombosed lumen, does not detect IH |

IH, intramural hematoma; AR, aortic regurgitation.

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It is important to define the anatomic site and extension of the dissection, the degree of AR, involvement of the coronary arteries, LV dysfunction, and the presence of PE or tamponade.

Intraoperatively, TEE is used during reconstructive surgery for hemodynamic status, entry/exit sites, evaluation of decompression of the false lumen, and assessment of concomitant valve surgery.[13] Postoperatively, TEE is used for the detection of residual regurgitation and LV dysfunction. TEE is also indicated for defining the anatomic site and size of aortic aneurysms.

## PERICARDIAL DISEASE

### Pericardial Effusion and Tamponade

Echo is the diagnostic test of choice for detection of PE and assessing its hemodynamic significance. TEE is usually superior to TTE for evaluating pericardial thickness and adjacent structures, although CT and/or MRI are preferred for evaluating the pericardium. Normally, the pericardial space contains 10 to 50 mL of fluid and the pericardium measures 1 to 3 mm in thickness. An increase in the volume of the pericardial fluid results in elevated pericardial pressures, leading to reduced RV filling, followed by reduced LV filling (Fig. 56-20). PE usually appears as an echo-free space surrounding the myocardium, although as protein or cellular debris increases in the fluid, it becomes increasingly echogenic.[35] PE is differentiated from pleural effusion by the anterior location of PE relative to the proximal descending thoracic aorta, while pleural effusion is located posterior to the aorta. Epicardial fat may be confused with PE, since it is also echolucent, although epicardial fat is usually more echogenic than pericardial fluid and is usually located anteriorly.[35] TEE is useful in the postoperative patient with tamponade and a small loculated PE that may be difficult to visualize on TTE. Loculated PE in postoperative cardiac surgery patients may cause tamponade in the absence of typical echo signs (Table 56-13). In these patients, any evidence of LA or LV collapse or other localized chamber compression may be indicative of hemodynamically significant elevated intrapericardial pressures.

**TABLE 56-12: True Versus False Lumen in Aortic Dissection**

| | True Lumen | False Lumen |
|---|---|---|
| Systole | Expansion | Collapse |
| Diastole | Collapse | Expansion |
| SEC/thrombus | Absent or minimal | Present |
| Blood flow | Systolic forward flow | Reversed or absent flow |

SEC, spontaneous echo contrast.

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### Constrictive Pericardial Disease

In constrictive pericardial disease, the visceral and parietal pericardium are adherent, thickened (>3 mm) and often calcified, which reduces ventricular filling in diastole and causes diastolic heart failure. However, the absence of pericardial calcification does not rule out the diagnosis of constriction. There are a number of causes of constrictive pericarditis and include repeated episodes of pericarditis, prior cardiac surgery, and radiation to the chest. The LV size, thickness, and function are typically normal. Multiple images should be taken in order to evaluate the thickness of the pericardium because it can be asymmetric. The IVC and hepatic veins will be dilated on subcostal views due to elevated RA pressure. Although echo signs of constriction (Table 56-14) are not very sensitive or specific, a completely

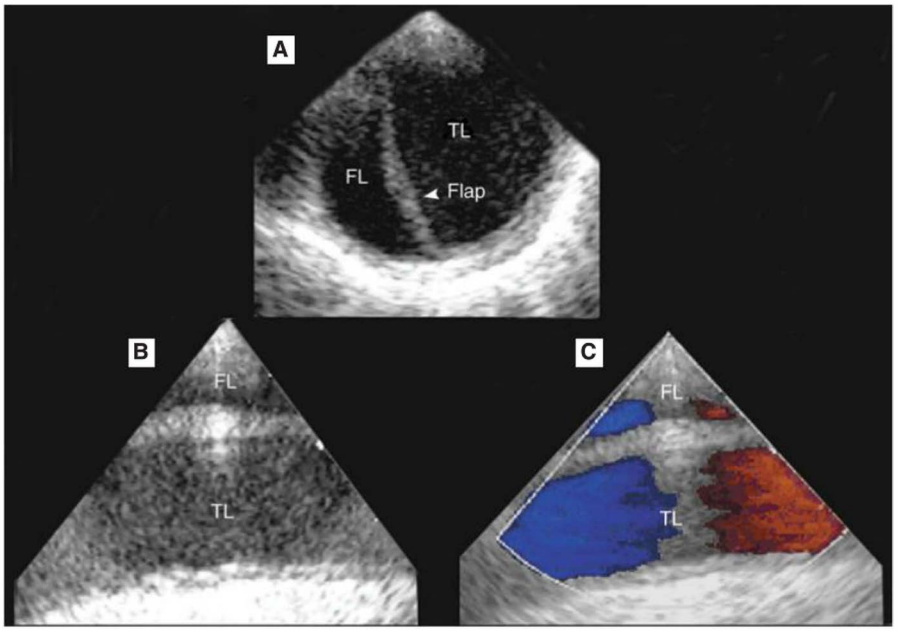



**FIGURE 56-19** Dissection of the descending thoracic aorta. Transesophageal echocardio-gram showing a large aortic dissection with t he diagnostic flap separating the true (TL) and false lumen (FL). **A.** Short-axis view. **B.** Long-axis view. **C.** Long-axis with color-flow Doppler shows flow in both the true and false lumens.

normal echo study usually rules out constriction.[36] Other imaging modalities, such as CT or MRI, may be necessary to further evaluate the pericardium and distinguish constriction from restriction.

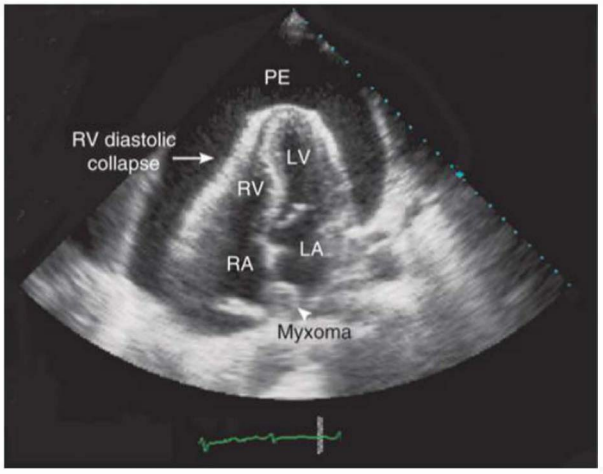



**FIGURE 56-20** Large pericardial effusion and cardiac tamponade. Transthoracic echocardiogram of the apical four-chamber view reveals an atrial myxoma attached to the interatrial septal with a large echolucent circumferential pericardial effusion (PE) and evidence of elevated intrapericardial pressure. Classic features of tamponade are shown with right ventricular (RV) diastolic collapse and abnormal interventricular septal motion (shifted toward the left during inspiration). RA, r ight atrium; LA, left atrium; LV, left ventricle.

## CARDIAC SOURCES OF EMBOLI

One of the most common indications for TEE includes the evaluation of cardiac sources of emboli, since TTE does not visualize well the potential sources of emboli (LA appendage thrombus, aortic atheroma, patent foramen ovale or atrial septal defect (ASD), LV thrombus, valvular lesions, intracardiac tumors). Small thrombi in the LA or LA appendage can be detected using TEE. In addition, factors that may contribute to or accompany atrial thrombi are often seen in the absence of an obvious thrombus: LA or LA appendage enlargement, SEC consistent with blood stasis, and decreased LA appendage contraction with low PW Doppler velocities (<20 mm/s). Aortic atheromas are evaluated for mobile components, plaque rupture, and ulceration and are graded as mild (<1 mm), moderate (1–3.9 mm), and severe (≥4 mm).

## ATRIAL SEPTAL DEFECTS

TEE is superior to TTE for visualizing ASDs. The anatomic defect is visualized using 2D echo and confirmed with Doppler and contrast (bubble study) using maneuvers that increase RA pressure, such as Valsalva or cough. The hemodynamic significance of the shunt is assessed using Doppler by quantifying the shunt size and determining the presence of pulmonary hypertension. Shunt quantification is obtained as the ratio of pulmonary-to-systemic flow ($Q_p$:$Q_s$) using Doppler cardiac outputs across the pulmonary valve and AV.[4] All four pulmonary veins should be visualized and

## TABLE 56-13: Echocardiographic Signs of Cardiac Tamponade

| RA Collapse | Sensitive But Not Specific |
|---|---|
| RV diastolic collapse | Ranges from inward dip to complete collapse of RV-free wall in diastole; specific sign but may be absent if elevated RV pressures or adhesions tether RV |
| LA, LV collapse | May be the only sign of tamponade in postoperative cardiac surgery patients |
| Abnormal interventricular septal motion | Inspiration: Septum shifts to the left |
| Respiratory variation in ventricular size | Inspiration: LV becomes smaller, RV larger |
| Respiratory variation in transvalvular inflow velocities | Inspiration: Mitral inflow E velocity decreases, tricuspid inflow velocity increases |
| Respiratory variation in PV and HV velocities | *Inspiration*: PV velocities decrease and HV velocities increase |
| Dilated IVC and blunted respiratory changes | Not very specific |

HV, hepatic vein; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PV, pulmonary vein; RA, right atrium; RV, right ventricle.

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## TABLE 56-14: Echocardiographic Signs of Constriction

| | |
|---|---|
| Pericardial thickening and calcification | TEE better than TTE, but additional imaging with CT or MRI may be necessary |
| Dilated RA, LA, IVC | Nonspecific findings |
| Diastolic flattening of the LV posterior wall | Secondary to reduced filling in mid–late diastole, sensitive but not specific |
| Abnormal interventricular septal motion | *Inspiration*: Septum shifts to the left |
| Premature pulmonary valve opening | RV diastolic pressure > PA diastolic pressure in middiastole |
| Respiratory variation in ventricular size | Inspiration: LV becomes smaller, RV larger |
| Respiratory variation in transvalvular and venous (pulmonary/hepatic) flow velocities | Similar to tamponade, respiratory variation may be more prominent in constriction |

IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

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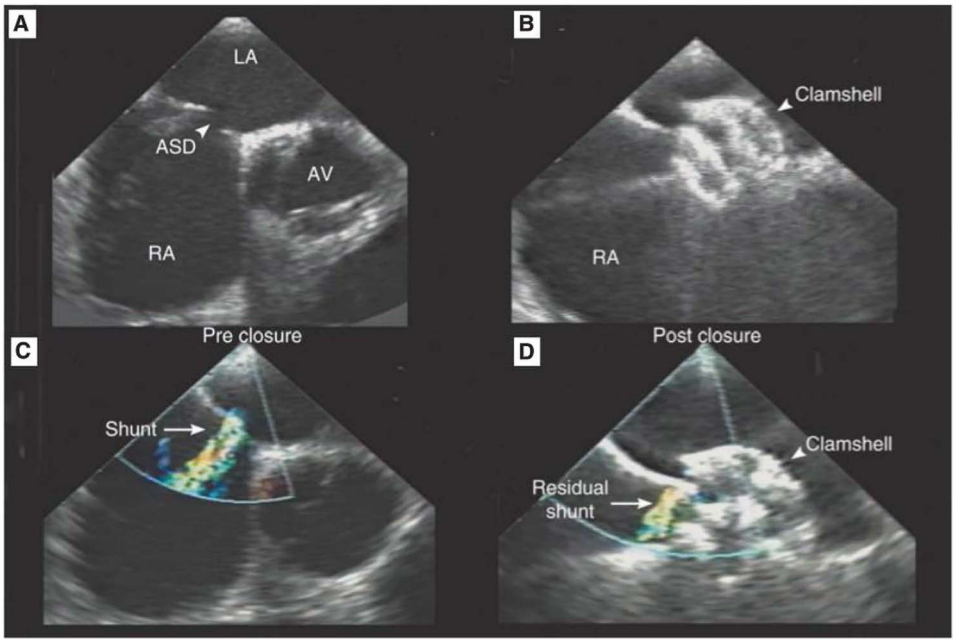



**FIGURE 56-21** Secundum atrial septal defect (ASD) and clamshell closure. **A.** Secundum ASD seen as a defect in the midinteratrial septum along with a dilated right atrium (RA) on transesophageal echocardiography. The size of the rim of tissue between the ASD and the aortic valve is critical in determining likelihood of success with device closure. **C.** Color-flow Doppler of the ASD shows a high-turbulence jet consistent with shunt (arrow). **B.** The clamshell has been deployed across the ASD. **D.** Postprocedure color-flow Doppler with small residual shunt that usually resolves spontaneously after a period of several weeks to months. AV, aortic valve.

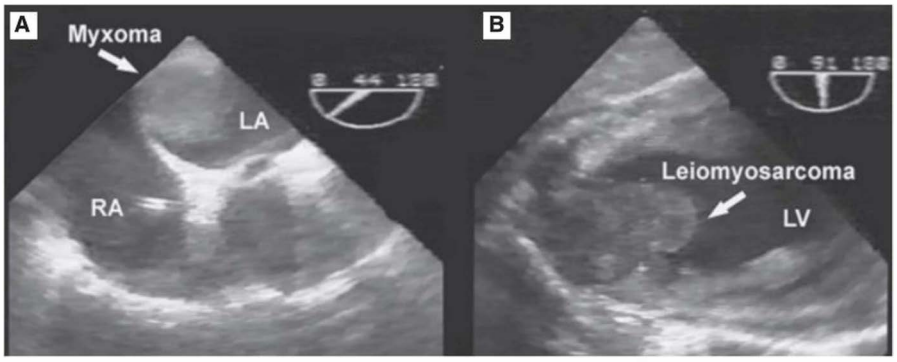



**FIGURE 56-22** Cardiac tumors. **A.** Large atrial myxoma attached to the interatrial septum, seen as a spherical mass with a speckled appearance. **B.** Metastatic leiomyosarcoma of genitourinary tract origin with myocardial invasion of the left ventricular (LV) apex.

the presence of associated anomalies excluded. TEE plays an important role in determining the suitability of ASDs for device closure versus cardiac surgery based on the size of the ASD and the rim of tissue surrounding it as well as the degree of septal tissue redundancy.[23] TEE has become essential for guiding placement of catheter-deployed closure devices and in assessing residual shunts (Fig. 56-21).

## CARDIAC TUMORS

TEE, because of its high sensitivity, is the imaging modality of choice and is superior to TTE, CT, MRI, and angiography for detecting cardiac tumors.[1,4] Although MRI may not detect small cardiac tumors, it is usually performed after TEE for further differentiation of thrombus (presence of methemoglobin or hemosiderin) from neoplasm, since it is superior to TEE for tissue characterization. MRI examinations are multiplanar and typically include fast T1- and T2-weighted techniques with administration of gadolinium (a paramagnetic contrast agent) and a technique for imaging moving structures with single-slice breath-hold, such as fast gradient-echo sequences (e.g., FLASH). Primary tumors are more likely to affect the myocardium, while secondary tumors usually involve the pericardium with secondary intramyocardial infiltation.[37] Atrial myxomas are the most common (up to 25 percent) primary cardiac tumors. Atrial myxomas as seen on TEE or TTE show several typical features[37] (Fig. 56-22A):

- Ninety percent originate in the interatrial septum, near the fossa ovalis.
- A spherical mass with a speckled appearance is often seen in RA myxomas, while a villous amorphous mass may be seen in LA myxomas.
- Ninety percent attach to the wall of the atrium via a stalk, which may allow prolapse through the MV.
- Intramural hemorrhage (cysts) and necrosis result in a heterogeneous appearance of echodensity; calcifications are uncommon but may be seen.
- They may be highly mobile and a cardiac source of embolus.

Metastatic tumors to the heart most commonly arise from the breast or lung but may include leiomyosarcoma (Fig. 56-22B). Metastatic tumors usually affect the pericardium and result in PE. In addition, some tumors metastasize through the IVC (renal cell, hepatoma), affecting the right heart more than the left; TEE allows for visualization of the route of extension.[37] Tumors involving the cardiac valves are rare (often fibroelastomas) and may affect valve competence and global LV function. MRI and ultrafast CT may be a useful adjunct in delineating tumors of the cardiac valves.[38]

## LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

TEE is used intraoperatively for septal myectomy for treatment of obstruction of the LVOT due to hypertrophic cardiomyopathy. SAM of the MV may cause LVOT obstruction; TEE is used to define the structures involved in the SAM (e.g., chordae, anterior leaflet). As in AV, LVOT gradients may differ intraoperatively versus preoperatively owing to different hemodynamics. CF Doppler typically demonstrates turbulent blood flow (mosaic pattern) at the site of LVOT obstruction. An eccentric jet of MR may also be seen if there is abnormal coaptation of the mitral leaflets (usually a posteriorly directed jet owing to abnormal coaptation of the anterior mitral leaflet).

TEE is also helpful during resection of lesions causing subaortic stenosis. It can determine the location and severity of obstruction. It is also useful for evaluating the success of the surgery in relieving the obstruction and in detecting MR that may result from the surgery.[22]

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## ECHOCARDIOGRAPHY IN CARDIAC SURGERY BOARD REVIEW QUESTIONS (CHAPTER 56)

1. Which is correct for assessment of LV regional wall motion by anesthesia?
   A. Normal ≥40 percent thickening
   B. Mild hypokinesis = 25 to 40 percent thickening
   C. Severe hypokinesis = 20 percent thickening
   D. Dyskinesis = paradoxical systolic motion
   E. Akinetic ≤10 percent thickening

2. Which is true regarding pulmonary vein flow on echocardiography?
   A. There are five velocities.
   B. $PV_a$ is related to left atrial contraction.
   C. Pulmonary vein systolic velocity peak greater than diastolic velocity peak suggests elevated left atrial pressures.
   D. Duration and peak $PV_a$ velocity are decreased in the setting of high filling pressures.
   E. Mitral inflow A wave duration greater than $PV_a$ duration indicates high left atrial pressures.

3. Which is an echo finding of severe MR?
   A. Regurgitant jet >20 percent of LA area
   B. Vena contracta >4 mm
   C. Eccentric wall-impinging jet
   D. LV end-diastolic dimension >60 mm
   E. LA dimension >4.5 cm

4. Which is an echocardiographic finding of severe AR?
   A. LV end-systolic dimension >50 mm
   B. Pressure half-time <300 ms
   C. Vena contracta >4 mm
   D. Systolic flow reversal in thoracic aorta
   E. Proximal regurgitant color jet/LVOT diameter >50 percent

5. Which is not an normal echocardiographic fining on a prosthetic valve?
   A. Regurgitant area of 1.5 $cm^2$ on aortic prosthesis
   B. Regurgitant jet length of 2.0 cm on mitral prosthesis
   C. Single central jet on Medtronic-Hall valve
   D. Four jets on St. Jude Medical valve
   E. Unequal jets on Bjork–Shiley valve

## ANSWERS

1. **Answer: D.** Dyskinesis is defined as paradoxical systolic motion. Normal function is >30 percent thickening, mild hypokinesis is 10 to 30 percent thickening, severe hypokinesis is <10 percent thickening, and akinesis is no thickening.

2. **Answer: B.** $PV_a$ (atrial flow reversal velocity) is related to left atrial contraction. There are four velocities measured on echocardiography—$PV_{S1}$, $PV_{S2}$, $PV_D$, and $PV_a$. Pulmonary vein systolic velocity peak less than diastolic velocity peak suggests elevated left atrial pressures. Duration and peak $PV_a$ velocity are increased in the setting of high filling pressures. $PV_a$ duration longer than the mitral inflow A wave duration indicates high LA pressures.

3. **Answer: C.** The echocardiographic findings of severe MR are regurgitant jet >40 percent of LA area, vena contracta >7 mm, eccentric wall-impinging jet, LVESD >45 mm, LVEDD >70 mm, LVEF <55 to 60 percent, dilated LA >5.5 cm, resting RVSP >50 mm Hg, restrictive mitral filling pattern, pulmonary vein systolic flow reversal, and ERO >0.4 $cm^2$.

4. **Answer: A.** The echocardiographic findings of severe AR are LVESD >50 to 55 mm, LVEDD >70 to 75 mm, LVEF <55 percent, pressure half-time <200 ms, proximal regurgitant jet width/LVOT diameter >65 percent, vena contracta >6 mm, holodiastolic flow reversal in thoracic aorta, and restrictive mitral filling pattern.

5. **Answer: A.** Normal amounts of regurgitation are found with most prosthetic valves. For an aortic prosthesis, the regurgitation area should be less than 1 $cm^2$ and length of the jet <1.5 cm. For a mitral prosthesis, the regurgitant area should be less than 2 $cm^2$ and length of the jet <2.5 cm. Characteristic flow patterns of specific valve types include one central jet for a Medtronic-Hall valve, two side jets and a central jet for a St. Jude medical valve, and two unequal side jets for a Bjork–Shiley valve.

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# Cardiac Magnetic Resonance Imaging

*Jens Vogel-Claussen*
*David A. Bluemke*

## INTRODUCTION

The availability of high-field-strength magnets, high-performance-gradient hardware, and ultrafast sequence technology in recent years has transformed cardiac magnetic resonance imaging (MRI) into a multifunctional tool. Cardiac MRI can provide three-dimensional analysis of cardiac anatomy, viability, motion, and function with high accuracy and reproducibility.[1,2] Because of the complexity of cardiac anatomy and motion, cardiac MRI can be challenging and previously had been performed primarily at specialized centers. More recently, a comprehensive cardiac MRI exam has become a reliable clinical tool in a wide range of healthcare centers. In this article, we briefly outline imaging techniques and illustrate the various applications of cardiac MRI.

## GENERAL PRINCIPLES

Communication between the surgeon and the MRI center is essential for efficient and accurate diagnosis. The examination will then be tailored to the specific clinical question. Instructing patients as to the nature of the examination will likely significantly improve the quality of the test. During the MRI examination, patients will need to perform multiple breath-holds of about 10- to 20-s duration. Patients with severe shortness of breath or who cannot lie flat on the MRI table are often poor candidates for cardiac MRI. Such patients should be discussed with the MRI center prior to referral. Overall, a directed examination requires about 20 to 30 min, whereas a comprehensive examination will require 45 to 60 min. There are no restrictions on eating or drinking before the MRI examination except if stress examinations are performed (see below).

### Contraindications

Compatibility of a patient's devices with the MRI scanner is a frequent issue and changes frequently with technology development. In general, all prosthetic cardiac valves are MRI compatible. Pacemakers and implantable cardioverters/defibrillators (ICDs) have previously been considered as strict contraindications to MRI. However, there have been recent reports at our institution and others of patients who have safely undergone MRI at 1.5 T magnetic field strength with certain types of these devices in place.[3,4] In these instances, imaging information from other techniques, such as computed tomography or echocardiography, was incomplete. Currently, MRI scanning with pacemakers or ICDs in place remains investigational. Older devices manufactured before the year 2000 and certain manufacturers' devices are less likely to be MRI compatible. Lower magnetic field strength (i.e., 1.5 T instead of 3 T) should also improve safety in conjunction with implanted devices. Thus, consultation with the MRI center should be performed when an MRI examination is deemed essential to patient care.

Coronary and other vascular stents are increasingly common. Most stents have not been explicitly tested by the manufacturer for MRI compatibility. Package labels from the manufacturer may indicate that MRI may be performed 6 weeks after implantation, with the rationale that the stent is endothelialized at that time and less likely to move in the magnetic field. Our approach is to evaluate these devices on a case-by-case basis. In many instances, the risk of performing the MRI examination with such a device may be outweighed by the benefit of performing the examination. Lists of devices that have been tested for MRI compatibility have been published in the literature as well as listed on websites, such as www.MRIsafety.com.

There is no known adverse effect of MRI on the fetus; MRI examination is frequently preferred compared to imaging examinations using x-rays. The decision to scan during pregnancy should be made on an individual basis. The gadolinium-based contrast agents used for MRI cross the placenta, so deferring the examination to a later trimester or after the pregnancy would also reduce any potential risk.[5] If an MRI exam has to be performed during pregnancy, we usually can avoid giving MRI contrast agents to answer a specific clinical question in most patients at our center.

Patients with renal failure should not undergo gadolinium-enhanced MRI, because they are at risk of developing nephrogenic systemic sclerosis (NSF). NSF is a rare but potentially debilitating or fatal fibrosing condition that has recently been linked to gadolinium-based contrast agents. For patients with chronic renal failure, the FDA has determined that the risk is greatest when the estimated glomerular filtration rate (GFR) is less than 30 mL/min/1.73 $m^2$. The policy at our institution is therefore generally not to administer intravenous gadolinium-based contrast agents in patients with chronic severe renal failure (GFR less than 30 mL/min/1.73 $m^2$), acute renal failure or in patients on dialysis.[6]

If cardiac stress imaging is performed with dobutamine, adenosine, or dipyridamole, the patient should be questioned about relative contraindications to these agents and specifically counseled to avoid theophylline-containing drugs or foods for at least 24 h prior to the exam. A gadolinium-based contrast agent is frequently used in association with cardiac MRI. Reactions to the MRI contrast agent are very rare, but a prior severe reaction would constitute a contraindication to another contrast injection.

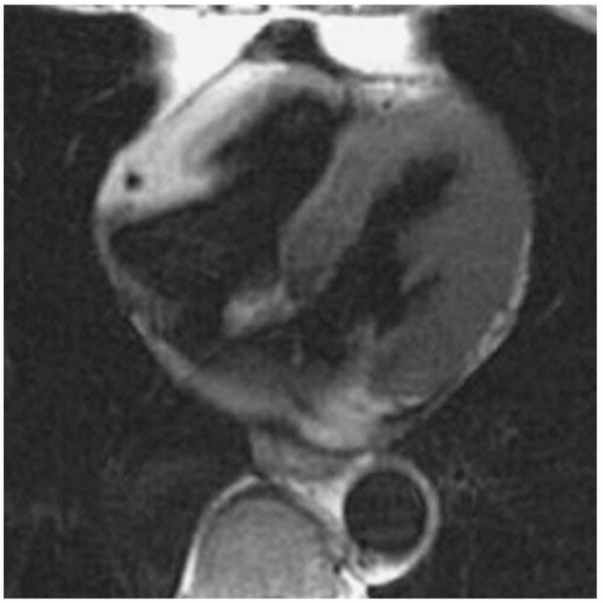


**FIGURE 57-1** Transverse black-blood MRI of the heart and descending thoracic aorta. Because of the double-inversion technique, the blood in the cardiac chambers and descending aorta appears black.

## Cardiac Gating

Cardiac MRI makes use of electrocardiographic (ECG) gating to suppress cardiac motion artifacts and arterial pulsation. The objective of cardiac gating is to acquire an R wave that is taller than the S or T wave. Even after obtaining a strong ECG signal initially, the signal may become obscured by additional noise from the magnetic field or regurgitant fraction (RF) pulses. Therefore optimal electrode-to-skin contact is necessary and skin shaving and cleansing is often necessary at the electrode placement sites. Nevertheless, imaging with an impaired ECG signal (i.e., pericardial effusion) or cardiac arrhythmias can be challenging.[7] For patients with arrhythmias who can tolerate β-blockade, a short-acting agent (e.g., metoprolol) may be administered 30 min before the MRI examination.

## Understanding Cardiac Magnetic Resonance Images

Terminology in MRI can be quite confusing to both the cardiovascular imager and the cardiovascular surgeon. The method of creating the images is termed the "pulse sequence," and pulse sequence names often change in order to give a manufacturer a perceived marketing advantage over competitors. Therefore a brief review of some principles underlying the terminology is worthwhile.

Images may be rather simply classified by the relative brightness of blood in the vessels or in the ventricular chambers. The blood can be made to be dark ("black-blood images") when the ventricular or arterial walls are the primary focus of the examination (Fig. 57-1). For example, to visualize a myocardial infarction, it is useful to make the blood in the ventricle very dark so as not to obscure the ventricular wall. Although it is entirely acceptable to refer to such images as "black-blood images," more specific terminology can be used to indicate how the image was generated. Thus, the term *black-blood image* is a very generic way of describing more specific terminology such as fast spin-echo or turbo spin-echo images.

The most important type of black-blood image generation for the cardiovascular system is termed a double-inversion recovery fast spin-echo sequence. These images are acquired in a breath-hold and are used to image myocardial edema, tumors, or complex anatomic regions. The method involves a specific pulse ("inversion pulse") that is used to make the blood dark relative to the myocardium. Advantages of the method include very high soft tissue contrast images, similar to those seen in brain or musculoskeletal imaging. Spatial resolution is usually quite good, between 0.5 and 2 mm. The disadvantage is a relatively long imaging time. In addition, the images are static rather than cine images.[8]

Black-blood magnetic resonance (MR) images can be further categorized. "T1-weighted" MR images display myocardium and fluid as intermediate signals and fat as bright signals. T1-weighted MR images are also used to show enhancement of abnormal tissues after intravenous administration of a gadolinium-based MR contrast agent (discussed further below). "T2-weighted" MR images show fluid and edema as bright signals. These are most commonly used to depict inflammation, tumor edema, or edema from myocardial infarction.

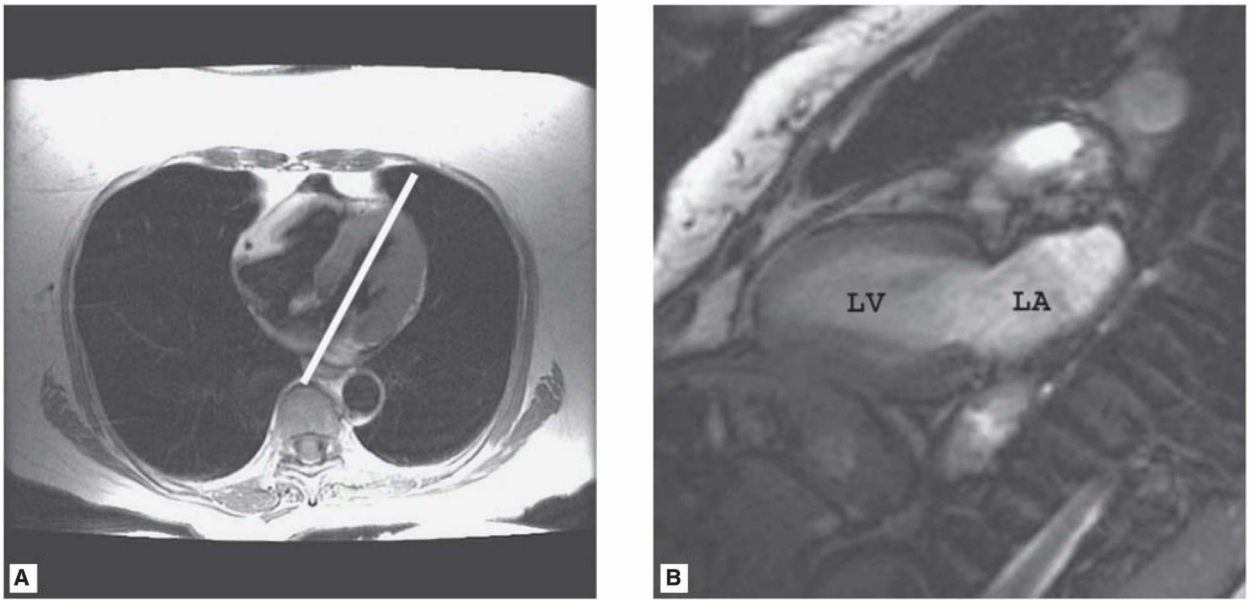



**FIGURE 57-2** By imaging in the plane through the left ventricle and left atrium prescribed by the white bar on the transverse view (**A**), an oblique vertical long-axis two-chamber view of the left ventricle and left atrium is obtained (**B**). The long-axis view is acquired with the bright-blood (FIESTA) MRI technique (B). LA, left atrium; LV, left ventricle.

Besides black-blood images, the most commonly used MR images are "bright-blood images" (Fig. 57-2). Typically, these are viewed as cine images of the ventricular or valvular planes. These methods have the advantage of taking less time to acquire than the black-blood images; thus visualization of motion is possible. The temporal resolution of these images is 25 to 50 ms or less if needed.

The bright-blood cine images are generated using a method generally known as gradient echo (GRE) imaging. The newest GRE methods have trade names such as balanced fast-field echo, FIESTA, or TrueFISP, depending on the vendor of the MR scanner. These sequences carry specific advantages for cardiac MR and represent a substantial improvement in image quality compared to older methods of cardiac cine imaging.[9] The spatial resolution of the images is about 2 mm, which is substantially greater than the resolution possible with nuclear techniques (6 mm). The blood pool in the ventricle has a very bright signal, so that the border between the ventricle and blood pool is easily distinguished. Turbulent jets at sites of stenosis or regurgitation are dark and readily distinguished using the newest sequences. GRE images are also used for imaging myocardial infarctions.

Disadvantages of bright-blood GRE images include large amounts of image distortion around metal, including sternal wire implants, stents, and embolization coils. The most frequent problem we have observed arose in patients with congenital heart disease who had embolization coils placed and required later evaluation with MRI. These coils distort large areas of anatomy, with the area of distortion centered on the device.

Other techniques—such as flow-sensitive MRI, myocardial viability techniques, and vascular imaging—are discussed later in this chapter.

## Cardiac Imaging Planes

Since the cardiac axes differ significantly from the axial, sagittal, and coronal planes of the body, specific imaging planes are necessary for adequate cardiac visualization and evaluation. Recently, three-dimensional acquisitions have been developed, so that the heart can be sliced and viewed from any desirable angle at postprocessing. This further shortens the acquisition time. A brief illustration of key imaging planes and how these images are derived is provided below.

### AXIAL, SAGITTAL, AND CORONAL PLANES

The first imaging plane is usually a transverse image of the chest with black-blood techniques (Fig. 57-1). Radiologists and surgeons are most familiar with this plane; it not only permits evaluation of the anatomic position of the cardiac chambers, coronary artery origins, and great vessels, but also detects extracardial intrathoracic pathology. Further sagittal and coronal planes can be obtained. The coronal plane is useful in evaluating the left ventricular outflow tract, aortic valve anatomy, diaphragmatic portion of the left ventricular wall, and the extension of the pericardium over the proximal portion of the great vessels. The plane parallel to the aortic arch on axial images is called the double-oblique or oblique sagittal plane. This plane is used to evaluate the aortic arch and aortic dissection.

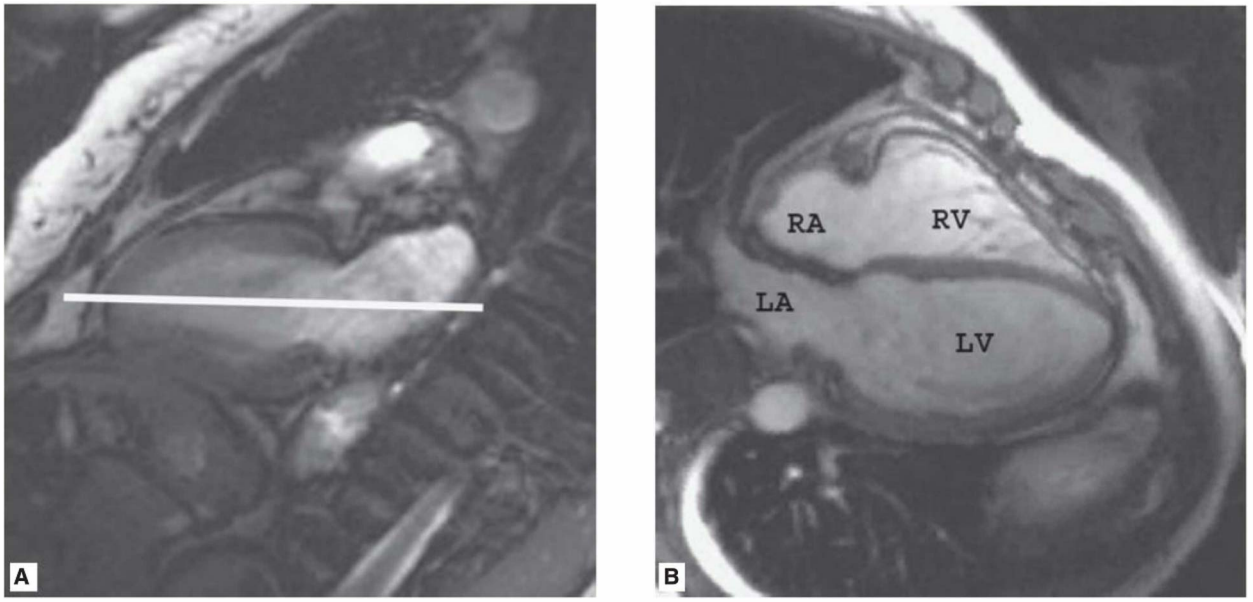



**FIGURE 57-3** By imaging along the axis prescribed by the white bar on the long-axis view (**A**), the horizontal long-axis view is obtained (**B**). The horizontal long-axis view is acquired with the FIESTA MRI technique. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

### VERTICAL LONG-AXIS VIEW

The vertical long-axis plane, sometimes referred to as a two-chamber view, is named based on visualization of the left ventricle and left atrium (Fig. 57-2A and B). The mitral valve is readily depicted in this plane.

### HORIZONTAL LONG-AXIS VIEW

The horizontal long-axis plane, sometimes referred to as a four-chamber view, is oriented 90 degrees to the vertical long-axis view. This view is obtained from a line drawn through the posterior wall of the left atrium, the middle of the mitral valve, and the left apex on the two-chamber view (Fig. 57-3A and B). The horizontal long-axis view depicts the right and left atria, both ventricles, and the mitral and tricuspid valves. This view also displays the relationship of the four chambers on a single image. Cine GRE images in this plane can evaluate mitral and tricuspid valve function, atrial or ventricular septal defects (VSDs), and bilateral ventricular contractions.

### SHORT-AXIS VIEW

Images in the short-axis plane are perpendicular to the left ventricular long axis seen on the horizontal or vertical long-axis views (Fig. 57-4A and B). The short-axis images show the cross-sectional anatomy of the right and left ventricle. Short-axis cine images are ideal to evaluate left and right ventricular mass, volumes, and function in order to obtain estimates of end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF). Differences in stroke volume from the left heart compared to the right heart quantify shunt volumes or valvular regurgitation. Furthermore, this plane is suitable for identifying focal wall motion abnormalities.

## CLINICAL APPLICATIONS OF CARDIAC MAGNETIC RESONANCE IMAGING

### Cardiac Mass and Function

Left ventricular mass is a strong independent predictor of fatal and nonfatal cardiovascular events.[10,11] Cardiac MRI is currently the most accurate and reproducible method for the assessment of cardiac volumes, mass, and function.[12] To evaluate the left ventricular mass, short-axis cine MR images are used. The endocardial and epicardial contours of the left myocardial wall are automatically or semiautomatically traced on each slice using special software. The contours of the cardiac chambers are then summed and multiplied by the slice thickness and slice gap (Simpson method) to obtain the contour volumes (Fig. 57-5). Finally, left ventricular wall mass is calculated from the volumes based on a myocardial density of 1.05 g/cm$^3$. By tracing ESV and EDV, cardiac function parameters like EDV, ESV, and EF can be calculated according to the same principle.

Cardiac MRI using bright-blood cine imaging is used to assess cardiac wall motion. Most centers grade wall motion visually, as either normal, hypokinetic, akinetic, or dyskinetic at the base, middle, and apex of the left ventricle. Qualitative

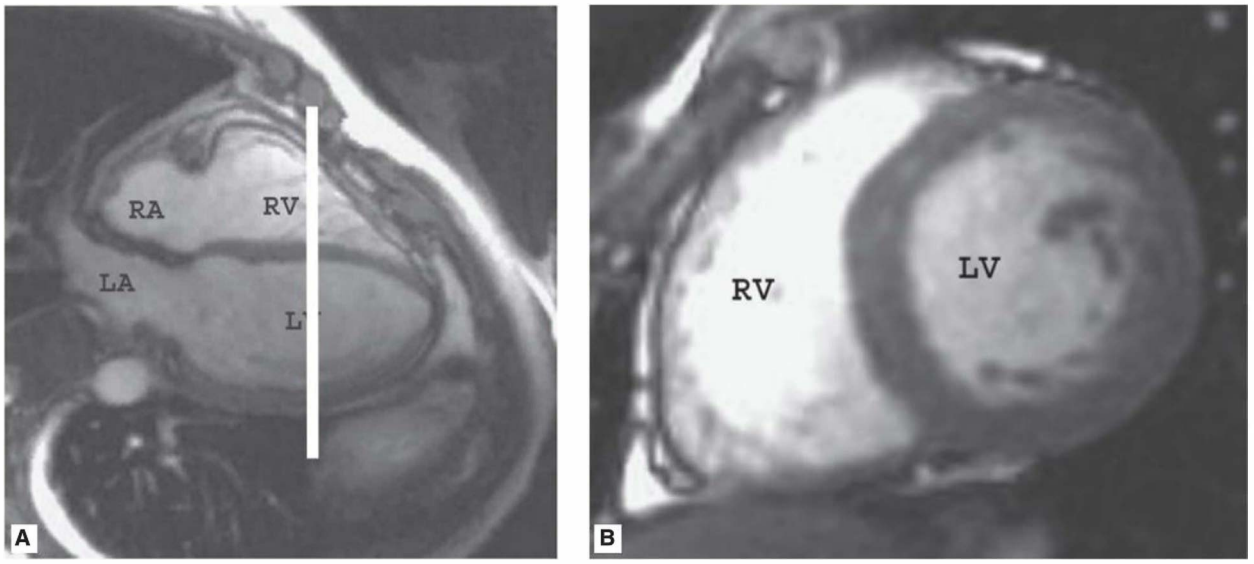



**FIGURE 57-4** By imaging along the axis prescribed by the white bar on the long-axis image (**A**), the short-axis view is obtained (**B**). The short-axis view is acquired with the bright-blood FIESTA MRI technique (**B**). RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

assessment of wall motion by MRI, like that of echocardiography, depends on the use of experienced readers for greatest reproducibility.

A limited number of centers have experience using "tagged MRI" to quantitatively measure regional cardiac wall motion. These methods, developed by Zerhouni and colleagues,[13] represent the most precise way for measuring both systolic and diastolic function. The method involves placing a magnetic strip on the myocardium at end diastole. As the heart contracts, the magnetic strip moves and bends along with the motion and contraction of the myocardium. Measuring the distances between the magnetic strips on each image assesses regional contractility. By using these methods, the contraction of the heart in any direction (circumferential, radial, and longitudinal) may be accurately measured (Fig. 57-6). Currently the primary use of quantitative methods to measure regional cardiac contraction has been in

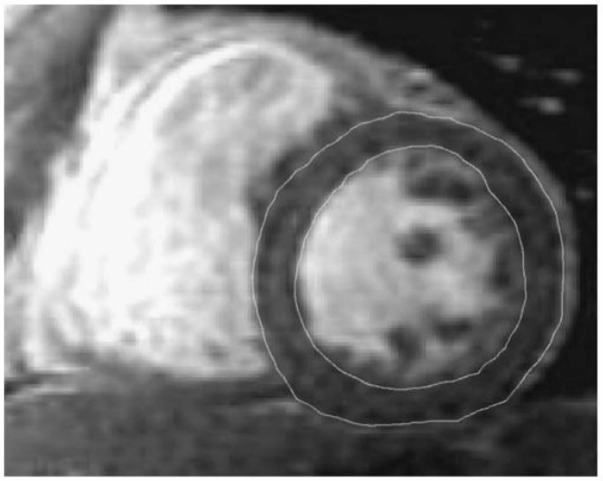


**FIGURE 57-5** Short-axis fast-gradient echo MRI demonstrates automatic outline of endo- and epicardial borders of the left ventricle for left ventricular mass evaluation with dedicated software.

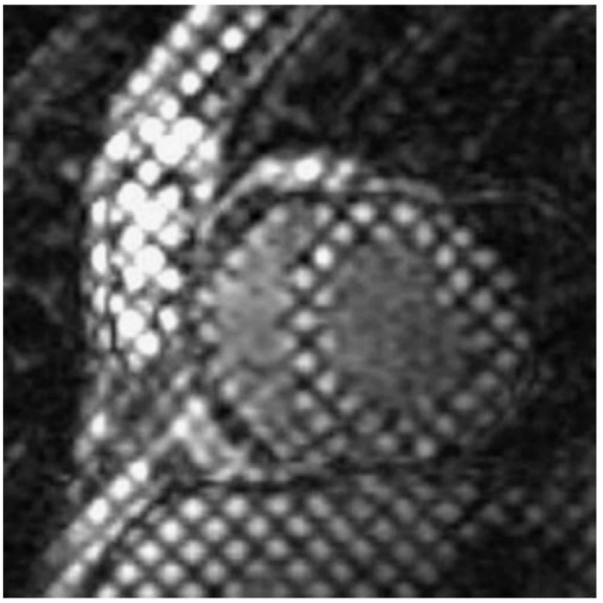


**FIGURE 57-6** To assess for focal wall motion abnormalities, MR tagging can be used, as demonstrated on this short-axis view of the heart. During myocardial contraction, the distance between magnetically placed tag lines decreases, directly measuring regional shortening.

specific research protocols. Given the nature of cardiovascular imaging, however, it is likely that these methods will gain further importance in the future. Tagged MRI has other specialized uses, such as the detection of pericardial to myocardial adhesions in constrictive pericarditis.

## Assessment of Valvular Heart Disease

Conventional and transesophageal echocardiography are still the most widely applied methods to evaluate valvular cardiac anatomy, such as leaflet quantity and thickness, vegetations, and valvular function. Recent developments in cardiac MRI techniques demonstrate that valve evaluation by MRI can be an attractive alternative or complementary to echocardiography. MRI evaluation is noninvasive and provides three-dimensional anatomic and functional data, which are potentially more accurate and reproducible than that of echocardiography.[14,15]

Black-blood sequences are used to analyze valvular anatomy (e.g., valve thickening or bicuspid valves). Cine MRI bright-blood techniques are used to evaluate abnormal flow patterns as seen in valvular stenosis or regurgitation, which cause loss of signal and appear as a dark signal void (Fig. 57-7). This signal void is caused by turbulent flow and the acceleration of flow within the normal bright-blood pool, similar to aliasing in Doppler ultrasonography. This signal void also depends on technical factors, which may vary in appearance depending on the MRI scanner. Thus, this signal void is usually evaluated only qualitatively. The degree of valvular regurgitation is measured by the area of the signal void volume and the maximum length of the signal void in the receiving chamber.

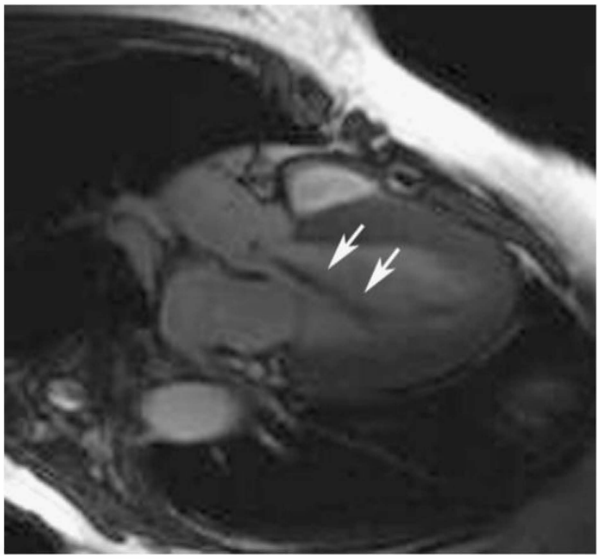


**FIGURE 57-7** Bright-blood (FIESTA) image of the heart demonstrates moderate aortic valve regurgitation (arrows).

A method to quantitate valvular regurgitation is to calculate the RF with ventricular volumetric measurements. As described above, end-systolic and end-diastolic volumetric measurements of the blood pool are first performed. In the normal heart, the right and left ventricular stroke volumes (EDV – ESV) are equal. If there is unilateral valvular regurgitation, the EDV is higher on the affected side than on the unaffected side of the heart; therefore the stroke volume on the affected side is also higher. The difference in stroke volume between a regurgitant and a normal ventricle is the regurgitant volume.

The RF can be calculated by dividing the regurgitant volume by the stroke volume of the regurgitant ventricle. An RF of 15 to 20 percent corresponds to mild valvular regurgitation; an RF of 20 to 40 percent to moderate regurgitation; and an RF of more than 40 percent to marked regurgitation. In the presence of unilateral combined valvular insufficiency (e.g., mitral and aortic regurgitation), this technique can calculate only the combined volume of regurgitation. In cases of bilateral valvular regurgitation (e.g., pulmonary and aortic valves), this technique will not provide accurate results. The method, however, may be used to assess the functional consequences of a VSD.

Flow-sensitive or velocity-encoded MRI is the best way to quantify valvular regurgitation. In this method, the velocity of blood flow is linearly related to the brightness of the MR image. Stationary tissue appears gray, whereas antegrade or retrograde flow along the phase-encoding axis appears as black or bright pixels. Velocity-encoded MRI makes it possible to quantify blood-velocity profiles at different time points of the cardiac cycle. Blood velocity can be encoded for imaging planes perpendicular to (through plane velocity measurement) or parallel to the direction of blood flow (in-plane velocity measurement). Flow–volume curves can map the absolute stroke volume and regurgitant volume in different phases of the cardiac cycle.

## Ischemic Heart Disease

Compared to nuclear medicine techniques such as single photon emission computed tomography (SPECT) or positron emission tomography (PET), cardiac MRI is capable of visualizing subendocardial or even papillary muscle infarctions owing to its superior spatial resolution.[16] Furthermore, cardiac MRI is more cost-effective than PET imaging.

## Myocardial Viability

Viable myocardium is myocardium that may recover function following coronary revascularization. Hibernating myocardium (with reduced blood flow) will recover function, but scar/fibrosis in an area of infarction will not. After myocardial infarction, accurate assessment of myocardial viability is crucial for optimal clinical decision making. Cardiac MRI is capable of accurately delineating nonviable or infarcted

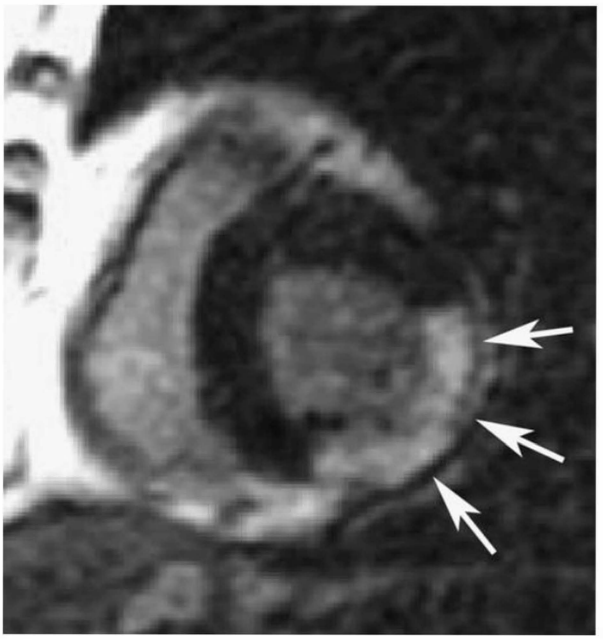


**FIGURE 57-8** Short-axis gadolinium-enhanced delayed MRI demonstrates transmural delayed enhancement of the myocardium in the distribution of the left circumflex coronary artery due to myocardial infarction (arrows).

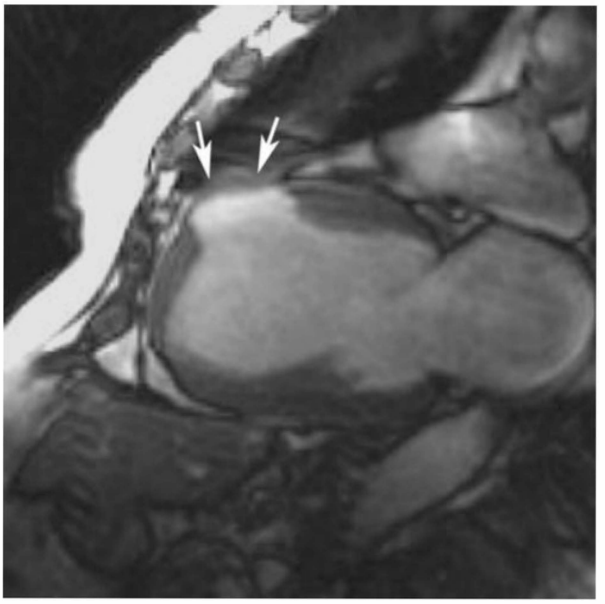


**FIGURE 57-9** Bright-blood (FIESTA) long-axis view demonstrates focal thinning and outpouching of the anterior left ventricular wall (arrows), compatible with aneurysm formation after myocardial infarction.

myocardium from potentially salvageable myocardium. The advantages of cardiac MRI as compared with nuclear, echocardiographic, or PET methods include (1) high spatial resolution, (2) lack of ionizing radiation, and (3) short examination time. Disadvantages include (1) reduced image quality in patients with arrhythmias and (2) patient safety exclusions, as discussed under "Contraindications," above.

For identifying viable versus nonviable myocardium, an intravenous injection of a gadolinium-based contrast agent is used. On delayed images, obtained 10 to 20 min after contrast injection, myocardial scar ("nonviable") retains the gadolinium contrast agent, while washout of the contrast agent occurs in viable myocardium (Fig. 57-8). MR images are optimized so that normal myocardium is "suppressed" on GRE images. Another commonly used term for MRI imaging of this type is *myocardial delayed enhancement* (MDE), or "viability" imaging. This terminology refers to the characteristic 10- to 20-min delay during which the contrast agent in scar/fibrosis distributes differently to normal, viable myocardium.

In viability imaging, scar/fibrosis is depicted as an area of high signal intensity that is typically subendocardial or transmural in a coronary artery distribution. Images are readily interpreted at the base, middle, and apex of the heart on short- and long-axis views. The concept that "bright is dead" is that myocardium with high signal on these MR images corresponds to noncontracting scar/fibrosis. The basis for this relates to both animal models following myocardial infarction and human studies that show lack of contraction of the enhanced myocardium following coronary revascularization.[17,18]

Because of the high spatial resolution of MRI, subendocardial and transmural infarction can be readily identified. In chronic myocardial infarction, myocardial scar may also show thinning of the ventricular wall, particularly in transmural infarction. In addition, thrombus in regions of aneurysm formation may be identified (Fig. 57-9). In general, myocardial scar/fibrosis involving more than 50 percent of myocardial wall thickness by cardiac MRI is unlikely to recover contractile function following coronary revascularization.[18]

## Acute Myocardial Infarction/ Myocardial Necrosis

With acute myocardial infarction, there is loss of integrity of myocyte cellular membranes. In addition, large myocardial infarctions may be associated with capillary occlusion and plugging with cellular debris, termed microvascular obstruction. This is more commonly observed in large Q-wave myocardial infarctions. Cardiac MRI may be used to image infarctions resulting in myocardial necrosis and microvascular obstruction. The MRI methods are similar as those described above for assessing myocardial scar/necrosis. In addition, MRI perfusion imaging is performed in order to assess microvascular obstruction.

After acute myocardial infarctions, first-pass perfusion images obtained immediately after bolus administration of the gadolinium contrast agent demonstrate lack of enhancement at the region of microvascular obstruction. This is typically at the "core" of the area of myocardial necrosis. Lack of enhancement of this infarct core, or microvascular obstruction, is related to poor patient prognosis, as documented by Wu and coworkers, with an increased incidence of congestive heart failure, recurrent infarction, and chest pain.[19]

The delayed-enhancement MR images in this setting typically show diffuse enhancement of the entire infarct area, or the zone of myocardial necrosis, which may be either subendocardial or transmural. The mechanism of enhancement is likely related to an increased volume of distribution of the gadolinium contrast agent due to disruption of cell membranes in the area of myocardial infarction. Areas of stunned myocardium, which have decreased function but intact cell membranes, do not show delayed enhancement on MRI. Cine MR images are obtained in conjunction with the delayed enhancement MR images and show akinesis in areas of myocardial stunning.

Note that areas of acute or chronic infarction may be difficult to distinguish using these methods. Both acute and chronic infarctions show bright areas on delayed enhancement MRI. If the infarction is transmural and chronic, the myocardium will show thinning. However, enhancement of the myocardium on MRI is very nonspecific and requires clinical correlation. Knowledge of the coronary catheterization results may aid in interpretation of the MRI results. For example, patients with large acute myocardial infarctions often have microvascular obstruction with delayed first-pass enhancement on MRI. However, a patient with a chronic infarction and total occlusion of a coronary territory may also show delayed first-pass enhancement in that coronary distribution. Both types of patients will have delayed enhancement on MR images obtained 10 to 20 min after injection of the gadolinium contrast agent.

If the clinical setting is ambiguous, T2-weighted images may be obtained for increased specificity for acute versus chronic infarction. T2-weighted MR images depict the distribution of edema in acute myocardial infarction, which is not present in scar/fibrosis.

## Myocardial Ischemia

Myocardial ischemia induced by exercise or pharmacologic stress may be evaluated using MRI.[20] The principles of these stress tests are identical to those used in nuclear medicine techniques except that exercise-induced ischemia is difficult to achieve in the MRI environment. MRI stress testing is currently done at relatively few institutions, although the results have rivaled those of nuclear pharmacologic stress testing. Advantages of MRI in this setting include a higher spatial resolution than can be obtained with nuclear methods (2 vs 6 mm, respectively); lack of false positives due to breast or soft tissue attenuation as seen with nuclear methods, and direct identification of myocardial scar/fibrosis with MRI. Compared to dobutamine stress echocardiography, MRI may be an alternative in patients with poor acoustic windows and indeterminate echocardiographic results.

MRI stress testing has been performed with dobutamine, dipyridamole, or adenosine as a pharmacologic stress agent. Dobutamine causes increased contractility of the myocardium. Ischemia-induced wall motion abnormalities at peak stress are readily visualized on cine MR images. In addition, chronic ischemic or hibernating myocardium will demonstrate increased contractility with dobutamine, resulting in improved wall motion in the affected areas compared to rest imaging. Dobutamine MRI is performed by performing MR cine imaging at increasing levels of dobutamine infusion, typically from 5 to 50 μg/kg/min. MRI must be performed rapidly in near real time and the examining physician must detect wall motion abnormalities, at which time the test is terminated.

Dipyridamole and adenosine are direct vasodilators. These agents result in augmented blood flow in normal coronary arteries, while stenotic vessels will show lack of increased blood flow. At our institution, we primarily administer adenosine to induce vasodilatatory stress, because of its short half-life and ease of use. For MRI stress perfusion imaging, we infuse adenosine intravenously at a rate of 140 μg/kg/min. At 2 to 3 min into the adenosine infusion, we inject a half dose of an MRI contrast agent through a separate intravenous line at a rate of 5 $cm^3/s$ and follow the contrast bolus with 3 to 6 short-axis fast GRE MR images, imaging the left ventricle as the contrast agent passes through the cardiac chambers and the myocardium with a temporal resolution of 1 to 2 heart beats. After about 10 min, we inject a second half dose bolus of contrast agent and apply the same short-axis GRE MR images to image the first pass of the contrast bolus at rest.

Transient ischemia can be detected as an area of myocardial hypoperfusion ("perfusion defect") during adenosine stress in a coronary artery distribution, which is reversible during rest (Fig. 57-10A–C). In a recent multicenter trial, the accuracy of adenosine stress perfusion MRI has been shown to be equal to or better than SPECT.[21] It also has been shown that the combination of stress perfusion MRI and *MDE MRI* improves the specificity of this test.[22] Stress first-pass perfusion MRI has also been used successfully in the emergency room setting in patients with chest pain and negative cardiac enzymes in order to triage and risk-stratify these patients, because the negative predictive value of a normal comprehensive stress MRI exam is high.[23,24]

## Coronary Artery Imaging

Direct visualization of the coronary artery wall and lumen is crucial for the diagnosis of coronary artery arteriosclerosis.

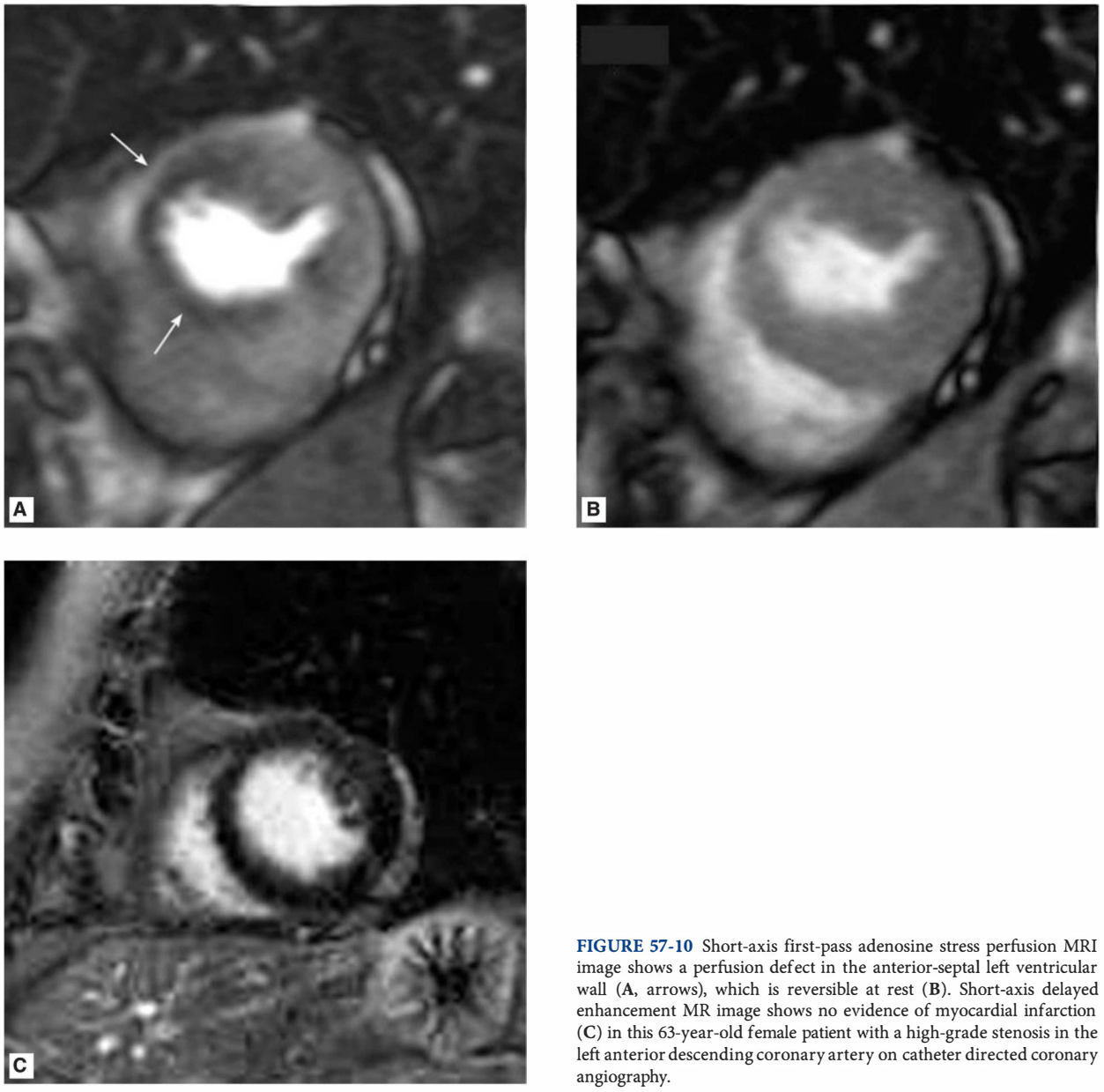



**FIGURE 57-10** Short-axis first-pass adenosine stress perfusion MRI image shows a perfusion defect in the anterior-septal left ventricular wall (**A**, arrows), which is reversible at rest (**B**). Short-axis delayed enhancement MR image shows no evidence of myocardial infarction (**C**) in this 63-year-old female patient with a high-grade stenosis in the left anterior descending coronary artery on catheter directed coronary angiography.

It is also necessary to determine the degree of luminal stenosis in evaluating a patient and planning treatment by coronary artery angioplasty, stenting, or bypass surgery. Conventional coronary digital subtraction angiography (DSA) remains the "gold standard" to visualize the coronary artery lumen and the degree of stenosis. However, this procedure is not risk-free, owing to its invasive nature. Furthermore, the cost of conventional angiography far exceeds the cost of coronary artery MRI.

In the last decade, MRI coronary angiography has made significant advances and demonstrated its feasibility.[25,26] At present, pilot studies with healthy volunteers can depict nearly the full length of the left circumflex, left anterior descending, and right coronary arterial lumen and wall (Figs. 57-11 and 57-12). The current spatial resolution ranges between $0.7 \times 0.7$ and $0.9 \times 0.9$ mm$^2$. However, in vivo coronary artery imaging can be challenging because of artifacts caused by complex cardiac, respiratory, and patient movement. For patients in a normal sinus rhythm, cardiac motion can be reliably suppressed by electrocardiographic gating. Respiratory gating can be challenging owing to more unpredictable diaphragmatic motion.

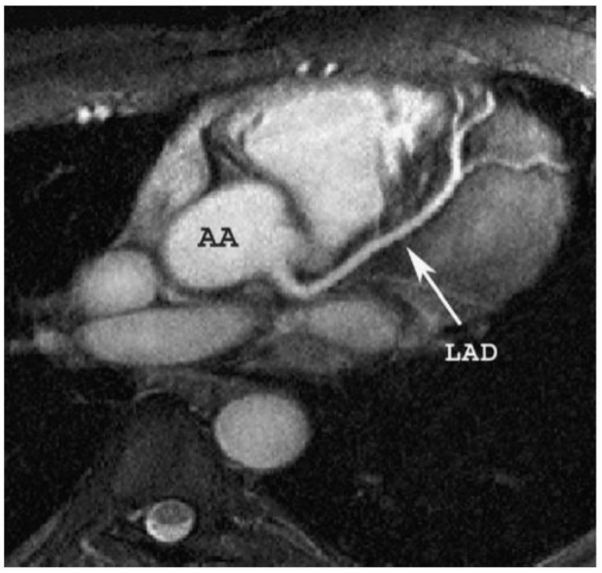



**FIGURE 57-11** Navigator free-breathing (3 T) MRI of the left anterior descending (LAD) coronary artery in a healthy volunteer. AA, ascending aorta. (Reproduced with permission from Stuber M, Botnar RM, Fischer SE, et al. Preliminary report on in vivo coronary MRA at 3 Tesla in humans. *Magn Reson Med* 2002;48(3):425–429.)

Several strategies have been pursued to minimize these factors. At present, three-dimensional GRE coronary MR angiography (MRA) techniques are the state of the art. Most recently, stronger field magnets (up to 3 T compared to most of the current 1.5-T MRI scanners) have become available commercially. These are likely to be applied to the challenging area of coronary MRI because they offer an improved tissue signals.[27]

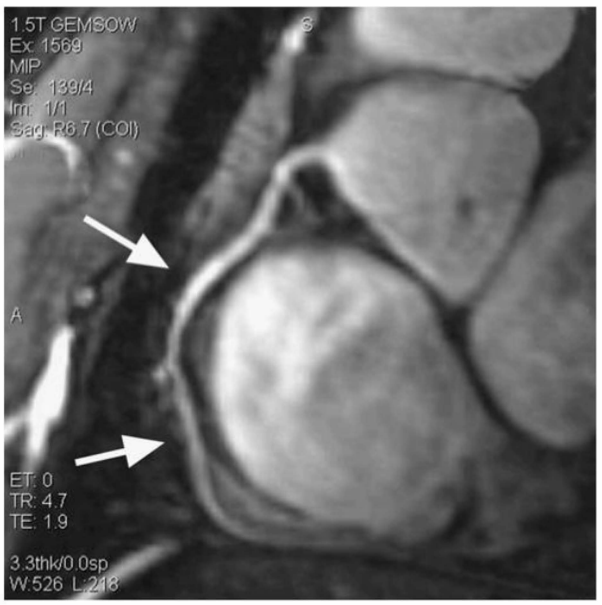



**FIGURE 57-12** A high-resolution MRI of the right coronary artery with intravenous contrast (arrows). (Reproduced with permission from Stuber M, Botnar RM, Fischer SE, et al. Preliminary report on in vivo coronary MRA at 3 Tesla in humans. *Magn Reson Med* 2002;48(3):425–429.)

Coronary artery calcifications may cause signal void and can mimic stenosis, although these effects appear to be less severe than with coronary CT angiography. Coronary artery bypass grafts and stents are difficult to evaluate because of artifacts from surgical clips, sternal wires, and stent material. Tantalum stents have more favorable MRI characteristics than stents made of stainless steel.

At present, the most common clinical indication for coronary MRA is the evaluation of aberrant coronary arteries. Knowledge of coronary anomalies is useful in planning cardiac surgery and in the prevention of sudden cardiac death (Fig. 57-13A and B). Coronary MRA has been proven to be equal or even superior to DSA in the analysis of congenital vascular anomalies and has become the gold standard for their evaluation. There may be an additional application in patients with Kawasaki disease in order to avoid repeat catheterization. Coronary MRA can reliably detect coronary aneurysms and is the preferred method for noninvasive follow-up of such patients (Fig. 57-14).[28]

## Magnetic Resonance Imaging of Cardiac Masses

MRI is the examination of choice to confidently exclude cardiac masses in cases where echocardiography is equivocal. MRI has superior tissue characterization capabilities to better define cardiac masses compared to cardiac CT imaging and does not require irradiation.

The most common cardiac mass is a ventricular or atrial thrombus. Acute thrombi may appear mass-like, whereas chronic thrombi conform to the contour of the cardiac cavity and may be more difficult to detect. The vascular supply of most thrombi is poor, so that the majority do not enhance after the administration of gadolinium contrast (Fig. 57-15).

Metastases to the heart and pericardium are 20 to 40 times more common than primary tumors and are generally associated with a poor prognosis.[29] Noncardiac tumors may spread to the heart or myocardium via hematogenous dissemination, lymphatic spread, direct local invasion, or via the transvenous route (Fig. 57-16). Tumors that most likely metastasize to the heart are malignancies of the lung and breast, melanoma, and lymphoma. Melanoma is the most common tumor metastasizing hematogenously to the heart. Melanoma metastases to the myocardium may show the characteristic MRI appearance of bright lesions on T1 and T2 images, which enhance with intravenous contrast. The brightness is attributed to paramagnetic metals bound to melanin.

MRI can depict direct invasion of the heart by bronchogenic or esophageal carcinomas, lymphoma, invasive thymoma, or mesothelioma. Obliteration of the pericardial fat plane by the tumor on MR images is a sign of involvement of the myocardium.

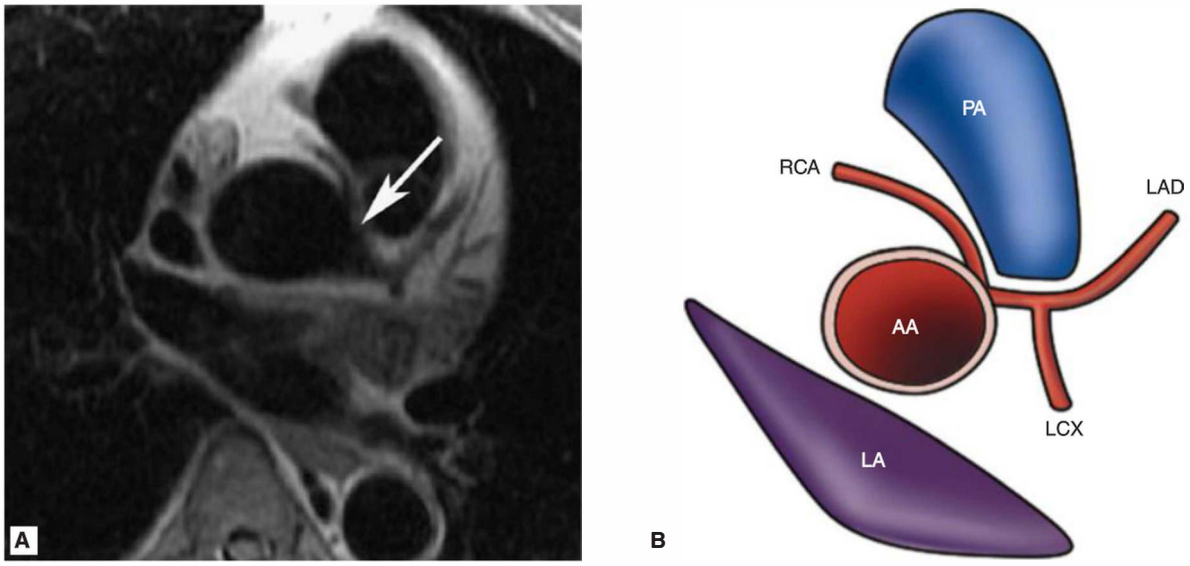



**FIGURE 57-13** A black-blood axial MRI demonstrating anomalous origin of the right coronary artery (arrow). The anomalous RCA travels between the pulmonary artery and the aortic root. This anomaly is potentially lethal and requires surgical reimplantation of the RCA (**A**). The anatomy is illustrated in the diagram (**B**). RCA, right coronary artery; LAD, left anterior descending coronary artery; AA, aortic artery; LCX, left circumflex coronary artery; PA, pulmonary artery; LA, left atrium.

Hepatocellular carcinoma, renal cell carcinoma, and adrenal tumors are the most likely to spread via direct extension into the inferior vena cava and the heart. Coronal and sagittal MRI is useful to depict this process. Gadolinium-enhanced MRI can further distinguish between tumor extension versus thrombus in the inferior vena cava and right atrium. In contrast to echocardiography, MRI can detect not only intracardiac but also extracardial masses, as found in the lungs.

Primary tumors of the heart are rare and most often benign. In general, most benign tumors are intralumenal

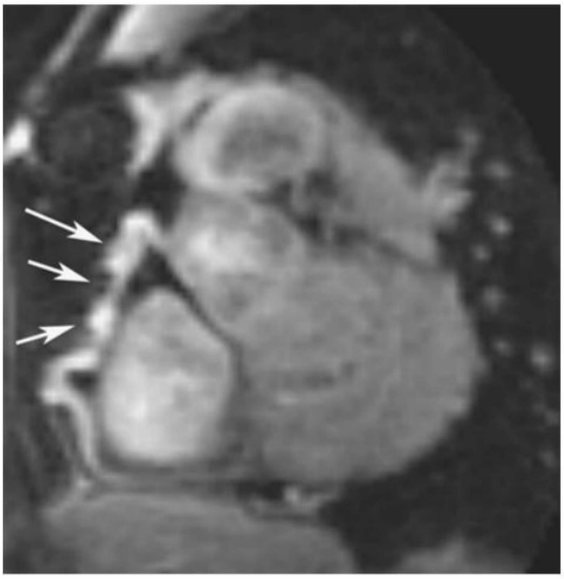


**FIGURE 57-14** This 16-year-old male presented with acute chest pain. Coronary MR angiography demonstrates aneurysmal dilatation and intermittent narrowing of the proximal right coronary artery (arrows) compatible with Kawasaki's disease.

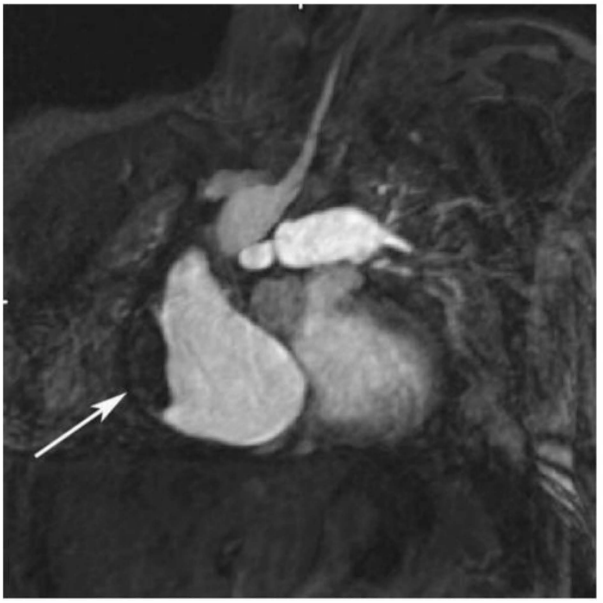


**FIGURE 57-15** This gadolinium-enhanced coronal oblique image demonstrates a nonenhancing mass in a patulous right atrium compatible with thrombus (arrow).

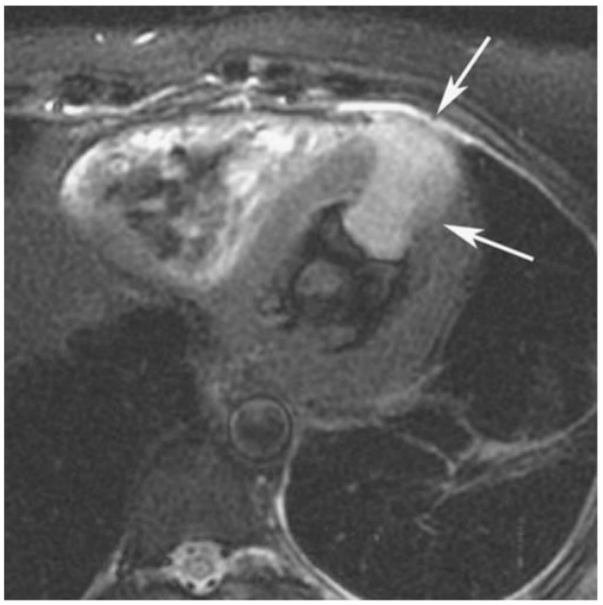


**FIGURE 57-16** Metastatic leiomyosarcoma involving the left ventricle. This axial cardiac black-blood MRI with fat suppression demonstrates a high-signal-intensity mass in the apex of the left ventricle (arrows). The tumor was resected surgically.

and are attached by a narrow stalk. Most malignant primary and secondary malignancies are broad-based or invade the myocardium. Most tumors enhance with intravenous contrast.

The benign cardiac myxoma is the most common primary cardiac tumor, representing 50 percent of all primary cardiac neoplasms.[30] It is usually located in the left atrium in the region of the fossa ovalis of the intra-atrial septum (Fig. 57-17A and B). The MRI appearance of cardiac myxomas varies depending of the amount of myxomatous and fibrous tissue. In general, myxomas will show increased T2 signals because of the myxomatous components of the tumor.

The second most common benign cardiac tumor is fibroma. It commonly arises from the interventricular septum, right ventricle, or atria and can be quite large. Because of their homogeneous fibrous nature, these tumors are hypointense on T2-weighted images and isointense on T1-weighted images, usually showing little or no contrast enhancement. Calcifications may occur; these are not well appreciated with MRI and are better evaluated by CT.

Cardiac lipomas usually occur in the pericardial space and less frequently in a cardiac chamber. Owing to their fat content, they have a homogeneous, bright T1 signal and usually do not enhance with intravenous gadolinium-based contrast agents. MRI can specifically identify fat because of the chains of fatty acid present; it is the method of choice to diagnose this tumor (Figs. 57-18A and B, and 57-19A and B). Paragangliomas are commonly located in the left atrium, coronary arteries, or aortic root. Characteristically, they show marked enhancement with gadolinium. Nuclear medicine imaging with iodine 123 or iodine-131 metaiodobenzylguanidine (MIBG) is also widely used to localize and diagnose extra-adrenal paragangliomas.[31]

Primary malignant cardiac tumors are extremely rare.[32] Angiosarcoma is the most common neoplasm of this kind, usually presenting as a bulky, infiltrative, right-sided cardiac mass, the right atrium being the most frequent site of origin (Fig. 57-20). Pericardial involvement is common,

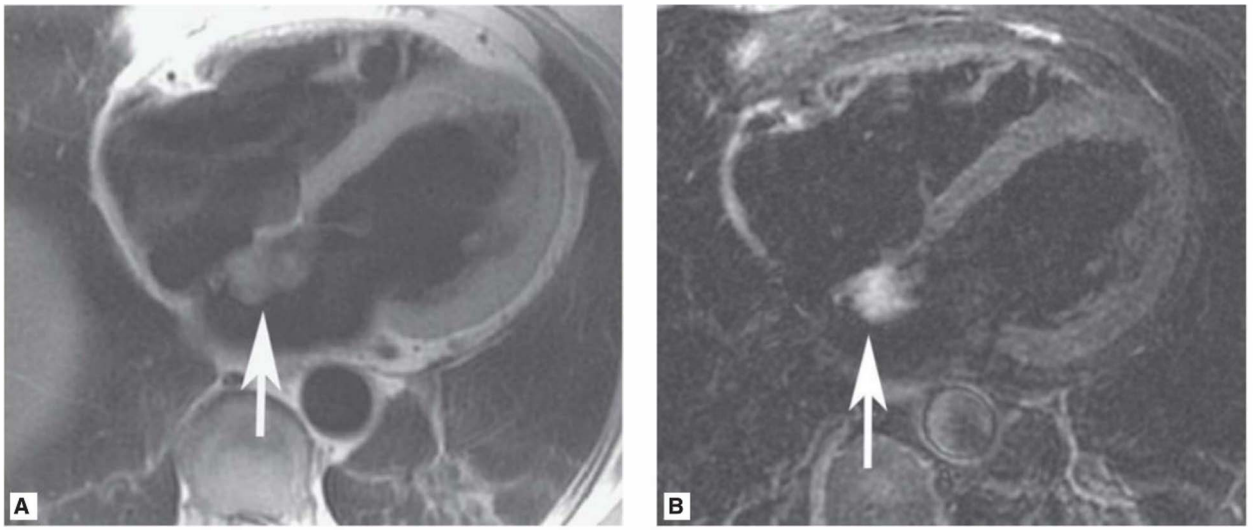



**FIGURE 57-17** Cardiac myxoma. This T1-weighted axial black-blood MRI of the heart shows a lobulated mass (arrow) in the left atrium arising from the atrial septum (**A**); it has high signal intensity on the fat-suppressed T2-weighted axial black-blood MRI due to the myxomatous component in this tumor (**B**).

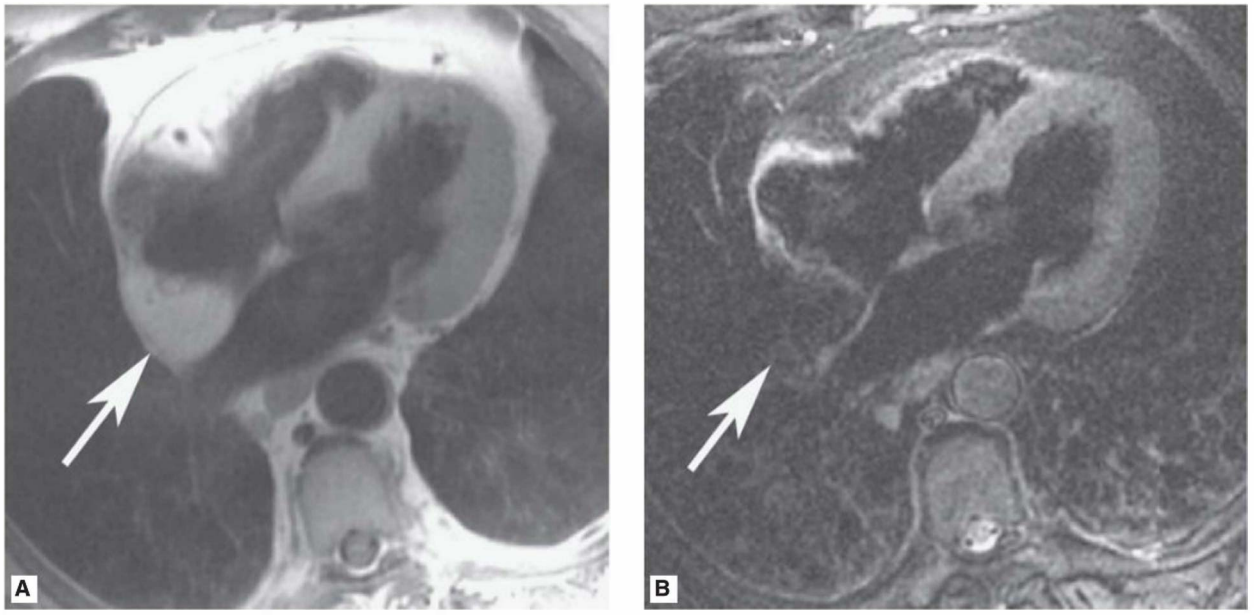



**FIGURE 57-18** This T1-weighted axial black-blood image without (**A**) and with (**B**) fat suppression demonstrates a paracardial lipoma (arrows). In B, the fat signal was selectively suppressed in a manner that is chemically specific for lipid.

and patients may present with a hemorrhagic pericardial effusion. Metastatic disease to bone, liver, adrenal gland, and spleen is often present at the time of diagnosis. Owing to their high vascularity, angiosarcomas enhance with gadolinium. Depending on the degree of tumor necrosis, MRI will show high signals in these areas on T2-weighted images. Rhabdomyosarcomas arise from cardiac striated muscle; their signal characteristics are similar to those of myocardium and they enhance after gadolinium administration. Leiomyosarcomas and fibrosarcomas are

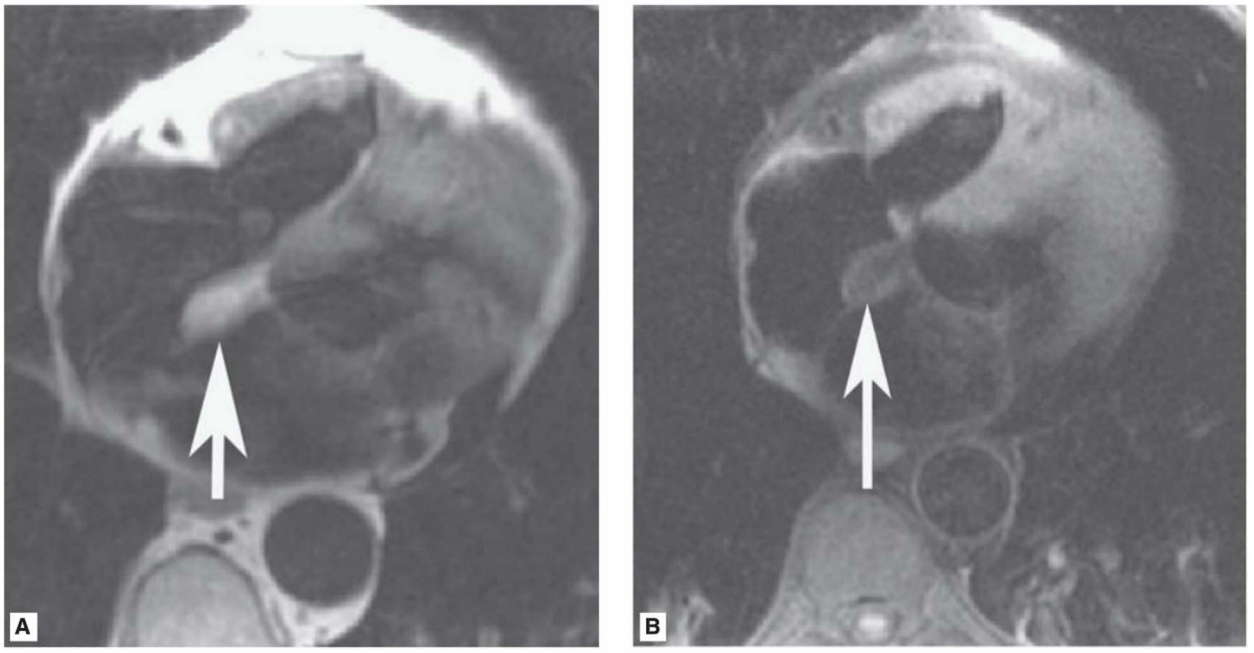



**FIGURE 57-19** Lipomatous hypertrophy of the atrial septum. This axial T1-weighted black-blood MRI demonstrates bright signal within a prominent atrial septum (**A**), which drops in signal with fat suppression (**B**).

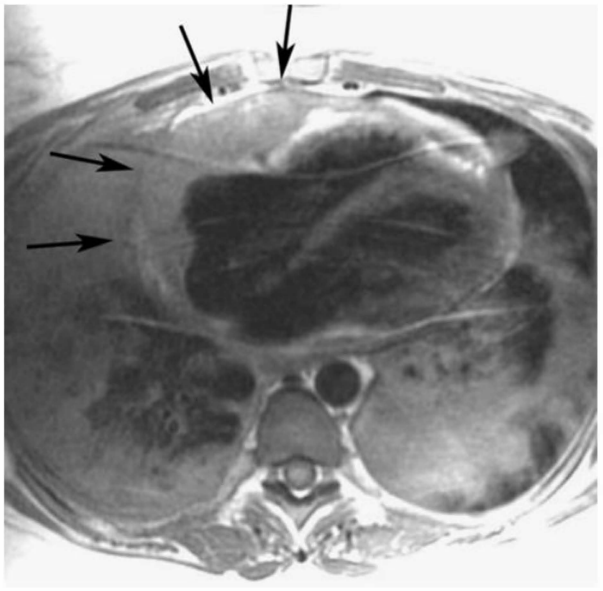


**FIGURE 57-20** Cardiac angiosarcoma. This T1-weighted axial black-blood MRI demonstrates an ill-defined mass (arrows) involving the right atrial and right ventricular wall (A), which avidly enhances with intravenous gadolinium. Note the pulmonary edema in both lower lungs.

exceedingly rare cardiac malignancies with variable signal characteristics and contrast enhancement.

## Pericardial Disease

The pericardium is a double-walled sac, of which the outer wall is fibrous. Beneath this is an internal sac called the serous pericardium, which consists of outer (parietal) and inner (visceral) layers separated by a potential space, the pericardial cavity. Echocardiography is usually the initial examination of choice to evaluate pericardial disease. MRI is complementary and more definitive in the evaluation of constrictive pericarditis, pericardial thickening, or loculated pericardial effusion.

The normal pericardium appears as a low-signal band around the heart usually measuring 1 to 2 mm in thickness; it is outlined by the high signal intensity of mediastinal and epicardial fat. The actual pericardium is thinner and measures about 0.4 to 1.0 mm. This discrepancy between MRI and pathologic measurements is likely due to a combination of chemical shift artifact (caused at fat–fluid interfaces), motion artifact, volume averaging, and the inclusion of small amounts of pericardial fluid in MRI measurements.[33] Small amounts of pericardial fluid also accumulate in the superior pericardial recess, a normal structure between the aortic root and main pulmonary artery, which should not be confused with a mass or focal aortic dissection.

Multiple pathologies can cause pericardial effusions. Pericardial fluid in excess of 50 mL is considered abnormal. Pericardial effusions are usually easily detected with ultrasound. However, loculated pericardial fluid or a limited acoustic window (e.g., in patients with chronic obstructive pulmonary disease) can make evaluation with ultrasound difficult. Simple effusions demonstrate low signal intensity on proton density–weighted spin-echo sequences or double-inversion sequences and high signal intensity on T2-weighted spin-echo, fast spin-echo, and steady state free precession (SSFP) as well as fast cine sequences. However, the movement of pericardial fluid during the cardiac cycle can result in signal void, especially on proton density–weighted and T2-weighted sequences. Hemorrhagic, proteinaceous, or exudative pericardial effusions often show increased signal intensity on T1-weighted images. Blood products of varying age within the pericardial space demonstrate variable T1 and T2 signals. Contrast enhancement with gadolinium may be seen in pericarditis or neoplastic effusions.

MRI findings of pericarditis include pericardial thickening of 4 mm or more and an associated simple or complex effusion. MRI is particularly helpful in diagnosing constrictive pericarditis; this is a common indication for MRI of the pericardium at our institution. The diagnostic hallmark of constrictive pericarditis in the correct clinical setting is pericardial thickening with or without calcifications (Fig. 57-21). Before antibiotic treatment was available, tuberculosis was the most common cause of constrictive pericarditis, often associated with large, extensive calcifications. Today, the most common cause of constrictive pericarditis is idiopathic (49 percent), followed by iatrogenic causes such as previous pericardiotomy (30 percent) and irradiation (11 percent).[34] Less common etiologies include viral pericarditis, connective tissue disease, neoplasm, and uremia. Gross calcifications are present in only 28 percent of cases of constriction. CT is more sensitive than MRI in detecting calcifications. However, owing to superior soft tissue contrast, MRI is superior in the distinction of pericardial thickening from

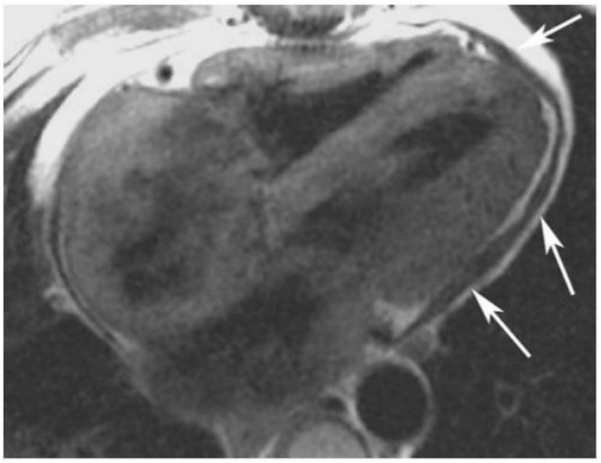


**FIGURE 57-21** Constrictive pericarditis. A T1-weighted axial black-blood MRI of the heart shows moderate thickening of the pericardium (arrows).

pericardial effusion. In a series of 29 patients with clinical symptoms, pericardial thickening determined by MRI was associated with constrictive pericarditis with a sensitivity of 93 percent.[35] However, constrictive pericarditis can be seen without evidence of pericardial thickening. Therefore, clinical history and additional findings (e.g., tubular ventricles, enlarged atria, focal contour deformities of the ventricles, enlarged inferior vena cava, ascites, and pleural effusions) are helpful.[36] Also, postoperative pericardial adhesions can be seen in the setting of constrictive pericarditis.

Pericardial cysts derive from embryonic pericardium, which is pinched off during development. The most common location is the right anterior costophrenic angle. Pericardial cysts have a thin, nonenhancing rim and are indistinguishable from bronchogenic cysts by MRI. If pericardial cysts contain simple fluid, they are dark on T1-weighted sequences and bright on T2-weighted images. If they contain proteinaceous fluid or blood products, they may have a bright signal on T1-weighted images.

Rarely, complete or partial absence of the pericardium occurs, and these conditions can be diagnosed by MRI. However, portions of the pericardium overlying the left lateral ventricle and right atrium may not normally be visualized. Partial absence of the pericardium can be challenging in these cases.

Metastatic pericardial involvement is far more common than primary pericardial malignancies and can be imaged with cardiac MRI.

## Magnetic Resonance Imaging of Congenital Heart Disease

Cardiac MRI complements echocardiography in the evaluation of congenital heart disease and provides explicit depiction of the morphology of the chambers and great vessels. Often MRI makes invasive angiocardiography in pediatric and adult patients unnecessary and decreases the morbidity in the diagnostic workup of these patients.

Dedicated imaging coils for infants for higher signal-to-noise acquisitions allow thinner slice selection and smaller fields of view for higher resolution. This improves image quality and the confidence in diagnosis of congenital heart disease. Single-breath-hold MRI is obtained in ventilated patients by suspending respiration for short periods.

For the evaluation of aortic coarctation, the oblique sagittal plane is most useful in defining the location and anatomy of the isthmus in relation to the aortic arch arteries (Fig. 57-22). Most frequently, gadolinium-enhanced three-dimensional MRA techniques are used to depict collateral circulation and vascular variants, such as a right aberrant subclavian artery. After surgical treatment, MRI is routinely used for postoperative follow-up. Other great vessel variants, such as double aortic arch, pulmonary sling, or transposition, are easily depicted with MRI (Fig. 57-23).

MRI of a patent ductus arteriosus can be challenging due to the generally small size, length, and orientation of

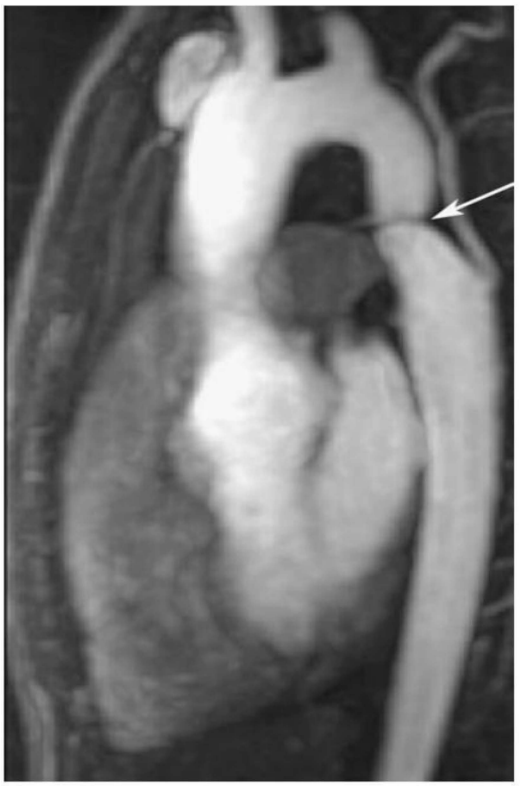


**FIGURE 57-22** A double-oblique MR angiogram of the aortic arch with intravenous gadolinium shows an aortic coarctation of the distal arch (arrow) with mild poststenotic dilatation of the descending thoracic aorta.



**FIGURE 57-23** Transposition of the great arteries. A multi-planar reconstructed gadolinium-enhanced MRI of the heart shows an anomalous pulmonary artery arising from the left ventricle (black arrow) and an anomalous ascending aorta arising from the right ventricle (white arrow).

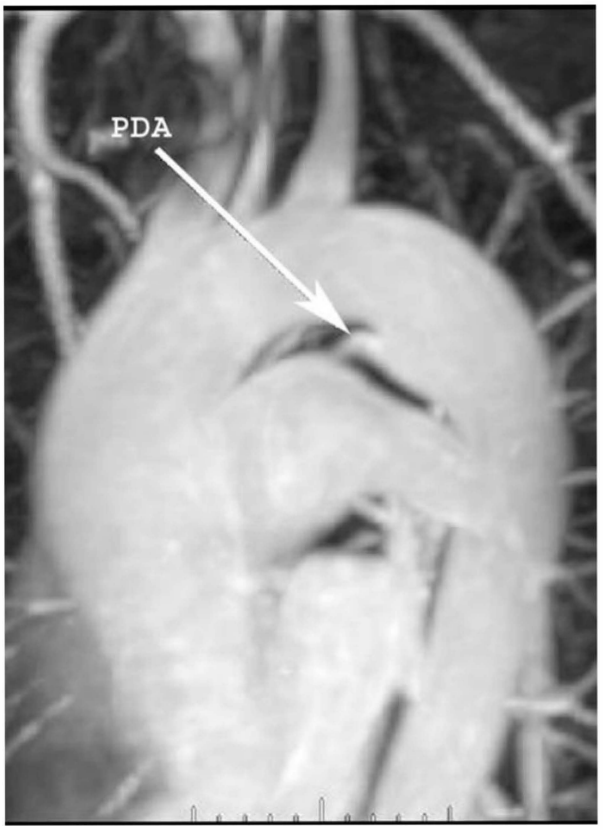



**FIGURE 57-24** Patent ductus arteriosus (PDA). A double-oblique MRI of the aortic arch with intravenous gadolinium shows a patent vascular connection (arrow) between the main pulmonary artery and distal aortic arch.

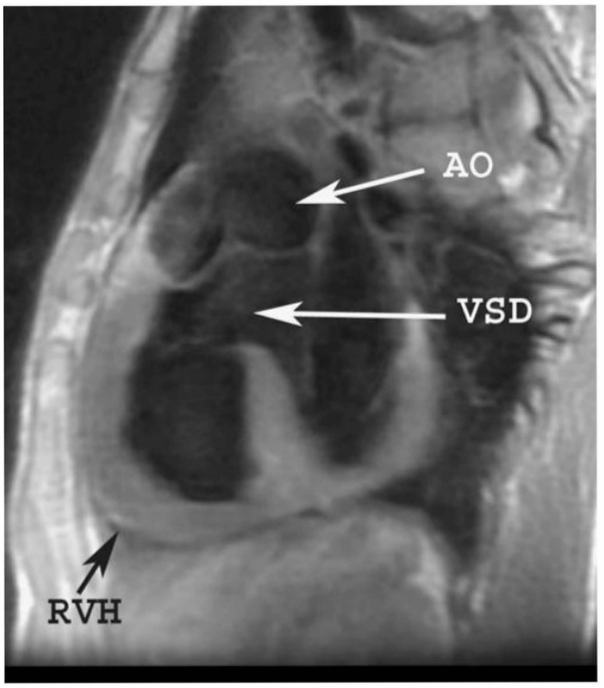



**FIGURE 57-25** Tetralogy of Fallot. A black-blood MRI of the heart demonstrates the key features of tetralogy of Fallot: a large ventricular septal defect (VSD), high-riding aorta (AO), and right ventricular hypertrophy (RVH) due to pulmonary artery stenosis.

the duct and limited MRI resolution (Fig. 57-24). Therefore optimized coils, software, and patient sedation, which are especially vital in newborns and infants, are necessary. On coronal imaging, communication between the underside of the distal aortic arch and the superior aspect of the origin of the left pulmonary artery is often demonstrated. Finally, flow-sensitive imaging (phase contrast-MRI) can further quantify the amount of shunting.

As in the evaluation of cardiac valves, the anatomy and severity of intracardiac shunts with depiction of changes in secondary chamber morphology (e.g., hypertrophy or dilatation) can also be obtained with MRI. Axial or left anterior oblique projections are useful for evaluating the intra-atrial septum. Axial MRI has a 97 percent sensitivity and 90 percent specificity for detecting atrial septal defects.[37] Often the atrial septum is infiltrated with fat, which produces good contrast in evaluating the signal void due to turbulent flow and the direction of shunt flow with bright-blood cine GRE or FIESTA MRI. Flow-sensitive imaging can further quantify the amount of shunting. Accordingly, membranous and muscular defects of the ventricular septal wall can be depicted with MRI. Muscular VSDs may be difficult to detect with black-blood imaging and may be diagnosed indirectly by signal-void jets of the shunted blood. Careful evaluation of cine images allows distinction between left-to-right, right-to-left, and bidirectional shunts.

MRI is capable of confidently diagnosing the tetralogy of Fallot anomaly (Fig. 57-25). MRI evaluation in these patients includes characterization of the VSD, degree of pulmonary stenosis and aortic insufficiency, as well as depiction of right ventricular morphology. The usually large subaortic VSD is well demonstrated in axial, long-axis, or sagittal views. MRI evaluation of flow dynamics across the VSD is very important to assess for Eisenmenger physiology (right-to-left shunting). Coronal imaging is useful in evaluating the extent of systemic-to-pulmonary artery collaterals and the degree of pulmonary artery stenosis. Sagittal views are helpful in examining the overriding aortic root and degree of aortic regurgitation. Furthermore, MRI is vital for the preoperative planning and postoperative evaluation of surgical shunts. For example, Blalock–Taussig shunts are best evaluated along the long axis of the graft.

In infants with Ebstein's anomaly, imaging is necessary to diagnose the anatomic displacement and malfunction of the tricuspid valve and degree of right-sided cardiac dilatation due to tricuspid valve insufficiency. Postoperative MRI is helpful in evaluating the artificial tricuspid valve as well as chamber morphology. Sometimes MRI imaging of artificial

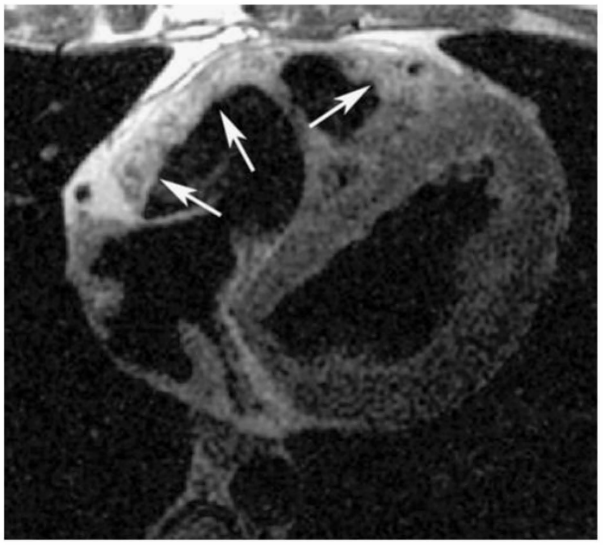


**FIGURE 57-26** Arrhythmogenic right ventricular dysplasia (ARVD). An axial black-blood cardiac MRI demonstrates fat infiltration and focal thinning of the right ventricular wall (arrows), key features of ARVD.

valves in postoperative hearts can be challenging owing to artifacts caused by artificial valves and surgical clips.

## Magnetic Resonance Imaging of Arrhythmogenic Right Ventricular Dysplasia

Arrhythmogenic right ventricular dysplasia (ARVD) is a rare disease in which tachyarrhythmias are associated with predominantly right-sided cardiomyopathy. These tachyarrhythmias are associated with sudden cardiac death. MRI is the preferred noninvasive imaging test for this condition.

The diagnosis of ARVD is challenging because clinical signs may be absent or ECG changes inconclusive. MRI findings in ARVD include an abnormal right ventricular myocardium with fatty infiltration and regional right ventricular akinesia or dyskinesia (Fig. 57-26).[38] Increased EDV and decreased right ventricular EF may also be observed. The high resolution of turbo spin-echo and double-inversion recovery images permits confident differentiation between epicardial fat, myocardium with trabeculations, and blood pool of the right ventricle. In addition, the high temporal resolution of cine GRE and SSFP images provides adequate temporal resolution of right ventricular wall motion abnormalities and permits calculations of EF and EDV.

## SUMMARY

Because of the high prevalence of cardiovascular disease and its socioeconomic impact, there is a need for improved means of noninvasive diagnosis. Cardiac MRI is a noninvasive technique that allows comprehensive examination of cardiac anatomy, function, and vasculature. With rapidly emerging and improving MRI techniques and the more widespread availability of this modality, cardiac MRI continues to play an important role in patient management.

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## CARDIAC MAGNETIC RESONANCE IMAGING BOARD REVIEW QUESTIONS (CHAPTER 57)

1. What is the purpose of delayed enhancement MRI?
   A. Identification of perfusion changes
   B. Delineation of myocardial edema due to contusion
   C. Coronary angiography
   D. Detection of myocardial scar and infarction (nonviable myocardium)
   E. Verification of CT coronary angiography

2. Patients undergoing gadolinium enhanced MRI are at risk for developing NSF if they have:
   A. Liver failure
   B. Heart failure
   C. Pancreatic insufficiency
   D. Renal failure
   E. Prior CVA

3. Valvular regurgitation is best quantified using:
   A. Delayed enhancement MRI
   B. Velocity-encoded MRI
   C. Bright-blood steady state free precession MRI
   D. T2-weighted MRI
   E. First-pass perfusion GRE MRI

4. Which is the best MR plane for imaging the mitral valve?
   A. Axial
   B. Coronal
   C. Double-oblique
   D. Vertical long axis
   E. Short axis

5. What MR sequence can be used to quantify regional wall motion?
   A. Steady-state cine MRI
   B. Tagged MRI
   C. Black-blood MRI
   D. Delayed enhancement MRI
   E. First-pass perfusion GRE MRI

## ANSWERS

1. **Answer: D.** For identifying viable versus nonviable myocardium, an intravenous injection of a gadolinium-based contrast agent is used. On delayed images obtained 10 to 20 min after contrast injection, myocardial scar (nonviable myocardium) retains the gadolinium contrast agent. Washout of the contrast agent occurs in viable myocardium. MR images are optimized so that normal myocardium is "suppressed" on GRE images. Another commonly used term for MRI of this type is MDE or "viability" imaging. This terminology refers to the characteristic 10- to 20-min delay during which the contrast agent in scar and fibrosis distributes differently compared to viable myocardium.
2. **Answer: D.** Patients with renal failure should not receive gadolinium enhanced MRI, because they are risk for developing NSF. NSF is a rare but potentially debilitating or fatal fibrosing condition that has recently been linked to gadolinium-based contrast agents. For patients with chronic renal failure, the FDA has determined that the risk is greatest when the estimated GFR is less than 30 mL/min/1.73 $m^2$.
3. **Answer: B.** Flow-sensitive or velocity-encoded MRI (phase-contrast MRI) is the best way to quantify valvular regurgitation.

4. **Answer: D.** The vertical long-axis view provides the optimal plane for mitral valve evaluation. The axial plane is best for the overall heart view and extracardiac structures. The coronal plane visualizes the left ventricular outflow tract and aortic valve. The double-oblique plane is best for the arch and evaluation of dissection. The short-axis plane is best for assessing wall motion abnormalities.

5. **Answer: B.** A limited number of centers have experience using "tagged" MRI to quantitatively measure regional cardiac wall motion. These methods represent the most precise way for measuring both systolic and diastolic function. The method involves placing a magnetic strip on the myocardium at end diastole. Measuring the distances between the magnetic strips on each image assesses regional wall contractility. The contraction of the heart in any direction (circumferential, radial, and longitudinal) can be accurately measured.

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III

# CONGENITAL CARDIAC SURGERY

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58

# Milestones in Congenital Cardiac Surgery

*Luca A. Vricella*
*Vincent L. Gott*
*Duke E. Cameron*

***"There is nothing more difficult to take in hand, more perilous to conduct, nor uncertain in its success, than to take the lead in the introduction of a new order of things. For the innovator has for enemies all of those who have done well under the old, and lukewarm defenders in all of those who may do well under the new."***

—Niccoló Macchiavelli (1469–1527)

Few other medical disciplines have required for their development the degree of daring courage, tenacity, and drive that characterized the efforts of the early pioneers in the field of congenital cardiac surgery. Only a century ago, Theodore Billroth publicly condemned the dream of cardiac surgical intervention by stating that "Any surgeon who wishes to preserve the respect of his colleagues would never attempt to operate on the heart."[1] Over the past six decades, the specialty of pediatric cardiac surgery has evolved from a heroic effort with occasional success into a consolidated, sophisticated specialty with excellent outcomes and, essentially, few limits imposed by pathology or age of the patient.

The history of pediatric heart surgery initially coincided with that of cardiac surgery itself. By far, the majority of early extra- and intracardiac procedures were in fact performed to address various forms of congenital (rather than acquired) heart disease. The adventure of intracardiac repair of congenital malformations, in turn, paved the way for technical advancements that pushed forward the field of adult cardiac surgery.

Each of the chapters in Part III of this book briefly touches on the historical highlights that pertain to specific malformations. In this chapter, the reader is offered a broad overview and key historical references that pertain to the initial evolution of this challenging field (Table 58-1), identifying four successive eras: (1) that of closed extracardiac operations; (2) the era of early closed or semiclosed intracardiac operations; (3) the initial phase of complete intracardiac repair; and (4) a subsequent period marked by the refinement of techniques and the expansion of the field to the correction or palliation of virtually any type of congenital heart disease.

## THE INITIAL PHASE: EARLY EXTRACARDIAC OPERATIONS

At a time when transpleural surgery was at its dawn,[2–4] the repair of simple cardiovascular malformations was a natural initial surgical goal. Although these conditions were anatomically simple, the too often advanced disease state of the patients and the threat of infection in the preantibiotic era often made these initial daring attempts unsuccessful.

John Strider of Boston first performed surgical ligation of a patent ductus arteriosus on March 6, 1937, immediately noticing that the palpable thrill had disappeared after duct interruption.[5] The 22-year-old patient was correctly diagnosed preoperatively with subacute bacterial endocarditis of the ductus arteriosus and succumbed to overwhelming sepsis on the fourth postoperative day. Necropsy disclosed a large endocarditic vegetation, extending from the arterial duct to the level of the pulmonary valve.

Robert Gross (Fig. 58-1) ushered in the field of congenital heart surgery by successfully interrupting a patent ductus arteriosus at Boston Children's Hospital on August 26, 1938.[6] Although he was the chief resident at the time, Gross performed the procedure in a very ill 7-year-old child, apparently against the advice of his chairman William Ladd.[7,8] The procedure took place while the latter was in Europe; the patient was uneventfully discharged in 10 days and survived for many years. Even though primacy of this milestone in cardiothoracic surgery has been debated,[9] this landmark operation demonstrates that intervention on the great vessels within the depth of the chest was possible, with curative outcome.

**TABLE 58-1: The Evolution of Cardiac Surgery: Time Line[a]**

1938—Ligation of patent ductus arteriosus (Gross)
1944—Coarctation repair (Crafoord)
1944—Blalock-Taussig shunt
1946—Potts' shunt
1946—Closed pulmonary valvotomy (Sellors)
1948—Blalock-Hanlon atrial septectomy
1952—Pulmonary artery band (Muller and Dammann)
1952—"Atrial well" technique for ASD closure (Gross)
1952—ASD closure with inflow occlusion and hypothermia (Lewis)
1954—Controlled cross-circulation (Lillehei)
1957—Pacemaker for complete heart block (Lillehei, Bakken, and Gott)
1958—Superior cavopulmonary anastomosis (Glenn)
1962—Waterston's shunt
1966—Balloon atrial septostomy (Rashkind)
1968—Atriopulmonary connection (Fontan and Baudet)
1971—Complex repair in neonates and infants with PHCA (Barratt-Boyes)
1975—Arterial switch operation (Jatene)
1976—Introduction of $PGE_1$ (Elliott)
1981—First-stage palliation of hypoplastic left heart syndrome (Norwood)
1984—Neonatal heart transplantation (Bailey)

$PGE_1$, prostaglandin $E_1$; PHCA, profound hypothermic circulatory arrest.
[a]Chronological sequence of major contributions to the development of the field of congenital heart surgery.



**FIGURE 58-1** Robert E. Gross (1905–1988). (From Westaby S. The foundation of cardiac surgery. *Landmarks in Cardiac Surgery.* Oxford, UK: Isis Medical Media Ltd, 1997:110. With permission.)

Following this initial procedure, coarctation of the aorta was addressed. Alfred Blalock was the first to attempt correction of this problem in a canine model, by turning down the distally transected left subclavian artery and anastomosing the vessel to the proximal descending aorta (Blalock-Park procedure).[10] A discouragingly high rate of paraplegia was noted, likely the consequence of relatively long clamp times, which limited flow through a normal-caliber subclavian artery and poor collateral circulation. Clarence Crafoord routinely clamped the aorta during ligation of the arterial duct, and first reported coarctation repair with end-to-end anastomosis in two patients operated at the Karolinska Institute in 1944.[11] Robert Gross described a case of successful coarctation repair shortly thereafter[12] and was first in addressing this malformation with an interposition homograft in 1949.[13]

These initial interventions were indeed curative, but the long-term outlook of children with complex cyanotic congenital heart disease remained dismal until the mid-1940s. Although somewhat approximative, preoperative diagnosis was possible and solely relied on clinical examination, chest radiographs, and electrocardiography; at Johns Hopkins, Helen Taussig was able, with such a rudimentary diagnostic armamentarium, to place children with congenital heart disease into broad diagnostic categories, underscoring the urgency of developing a method for stable palliation of cyanotic patients. The creation of an "artificial ductus arteriosus" was deemed unfeasible by Robert Gross; Taussig then turned to Alfred Blalock, the newly appointed chief of surgery at the Johns Hopkins Hospital (Fig. 58-2). While in Nashville, Dr. Blalock and Vivien Thomas (his laboratory technician) had established an experimental model of pulmonary hypertension that entailed ligation of the left pulmonary artery and anastomosis between the left subclavian and left branch pulmonary arteries.[14] Although they were unable to augment pulmonary pressure because of the low impedance of the pulmonary vascular bed, the technique provided the increase in pulmonary blood flow that cyanotic children so desperately needed. This concept was introduced in the clinical arena on November 29, 1944, when Blalock successfully performed the first systemic-to-pulmonary artery shunt, thus opening the doors to long-term palliation for cyanotic patients (Fig. 58-3).[15,16] Eileen Saxon, then a 16-month-old infant with pulmonary stenosis (Fig. 58-4), had barely reached the operative weight of 4 kg from a nearly prohibitive birth weight of 1.1 kg.

Several modifications of this initial concept have followed and were all eventually rendered obsolete by the introduction of the "modified" Blalock-Taussig shunt.[17] Among these, anastomosis of the descending aorta to the left pulmonary artery (Potts shunt)[18] and of the ascending aorta to the right pulmonary artery (Waterston shunt)[19] was reported in 1946 and 1962, respectively. These approaches often proved to be unreliable in regulating pulmonary blood flow, and were extraordinarily difficult to control at the time of late complete intracardiac repair.

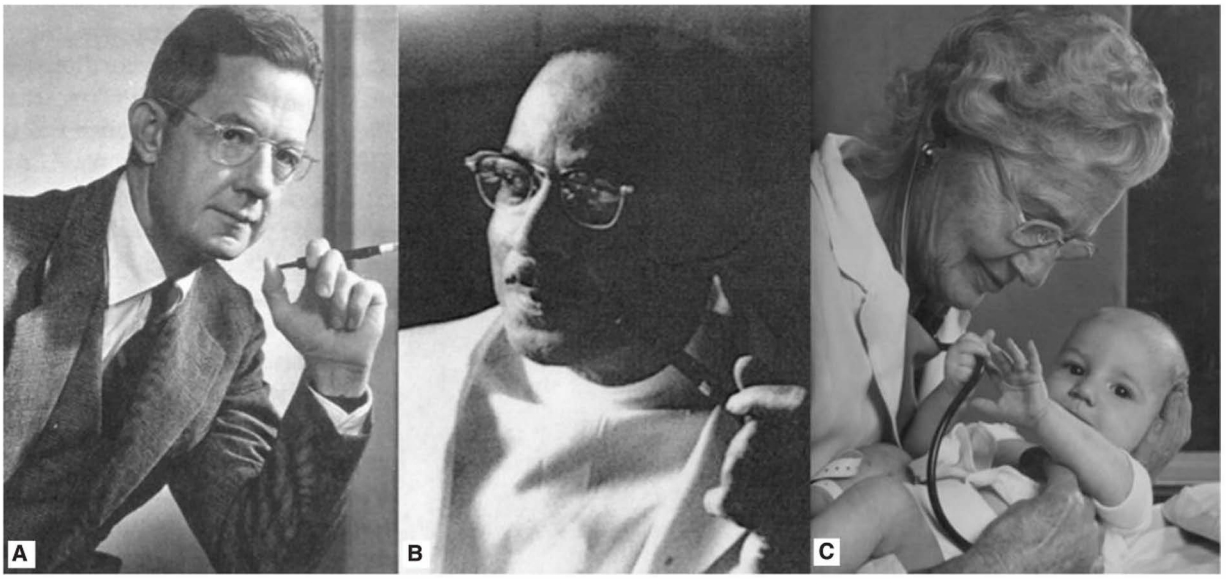



**FIGURE 58-2** Protagonists of the first systemic-to-pulmonary shunt on November 29, 1944, at the Johns Hopkins Hospital. Left to right: Alfred Blalock (1890–1964), Vivien Thomas (1910–1985), and Helen Taussig (1898–1986). (**A, C**: Copyright estate of Yousuf Karsh, Courtesy of Johns Hopkins University Photographic Archives; **B**: Courtesy of the Johns Hopkins University photographic archives.)

Over the ensuing decades, systemic-to-pulmonary shunts—rather than the initial approach to staged repair of biventricular hearts—became the mainstay of palliation for univentricular heart disease (Fig. 58-5). Extracardiac palliative procedures are now more typically performed as the initial step toward achievement of complete right heart bypass, the so-called Fontan circulation (Fig. 58-6).[20–26]



**FIGURE 58-3** One of the first "blue baby" operations at the Johns Hopkins Hospital, circa 1945. In the center of the photograph, to the left of the operating table, Dr. Alfred Blalock. Behind him, Vivien Thomas, and, to his left, the then chief resident Dr. William Longmire. Standing as first assistant, opposite to Dr. Blalock, is the assistant resident, Dr. Denton Cooley. (Courtesy of the Johns Hopkins University photographic archives.)



**FIGURE 58-4** Eileen Saxon, the first infant to undergo a systemic-to-pulmonary shunt for palliation of cyanotic heart disease. Note the left-sided thoracotomy scar. In the first few patients undergoing the procedure, the thoracotomy was performed on the side ipsilateral to the aortic arch. The technique very rapidly evolved to a turndown of the subclavian artery contralateral to the side of the aortic arch, as technically more straightforward. (WP Longmire. *Alfred Blalock. His Life and Times.* Privately published by the author, 1991: 99. With permission.)

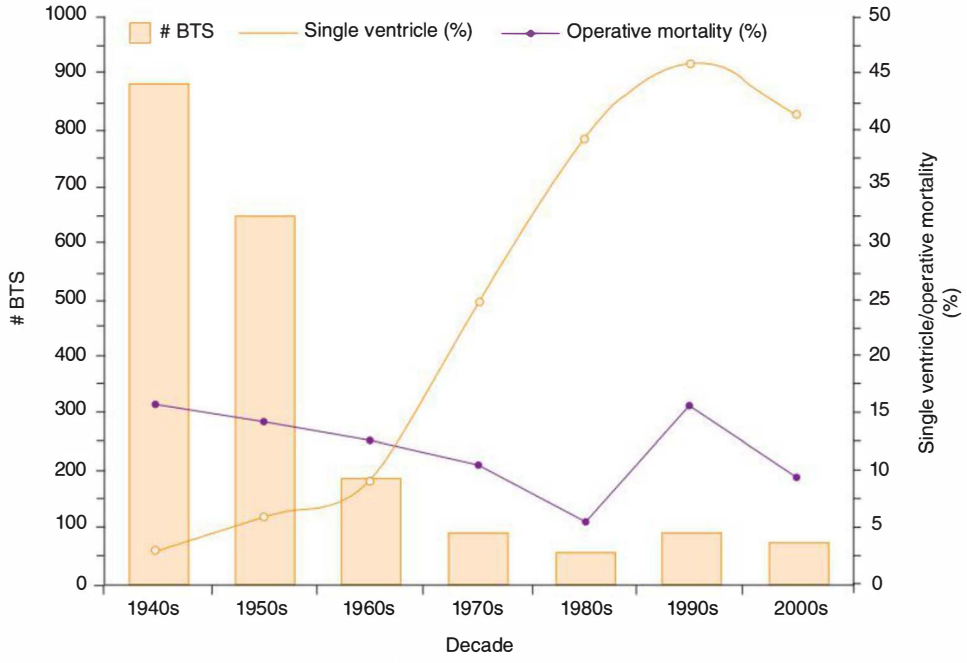



**FIGURE 58-5** Trends in systemic-to-pulmonary shunts: the Johns Hopkins experience with 2029 shunts over six decades (1944–2006). A decrease in the total number of procedures is paralleled by a rise of the percentage of shunts performed as palliation for univentricular heart disease. A reduction in mortality and the subsequent peak in the late 1980s and early 1990s is possibly related to shunts being mainly utilized as part of the initial treatment of hypoplastic left heart syndrome. (Reproduced with permission from Williams JA, Bansal AK, Kim BJ, et al. Two thousand Blalock-Taussig shunts: a six-decade experience. *Ann Thorac Surg*. 2007;84(6):2070-2075.)

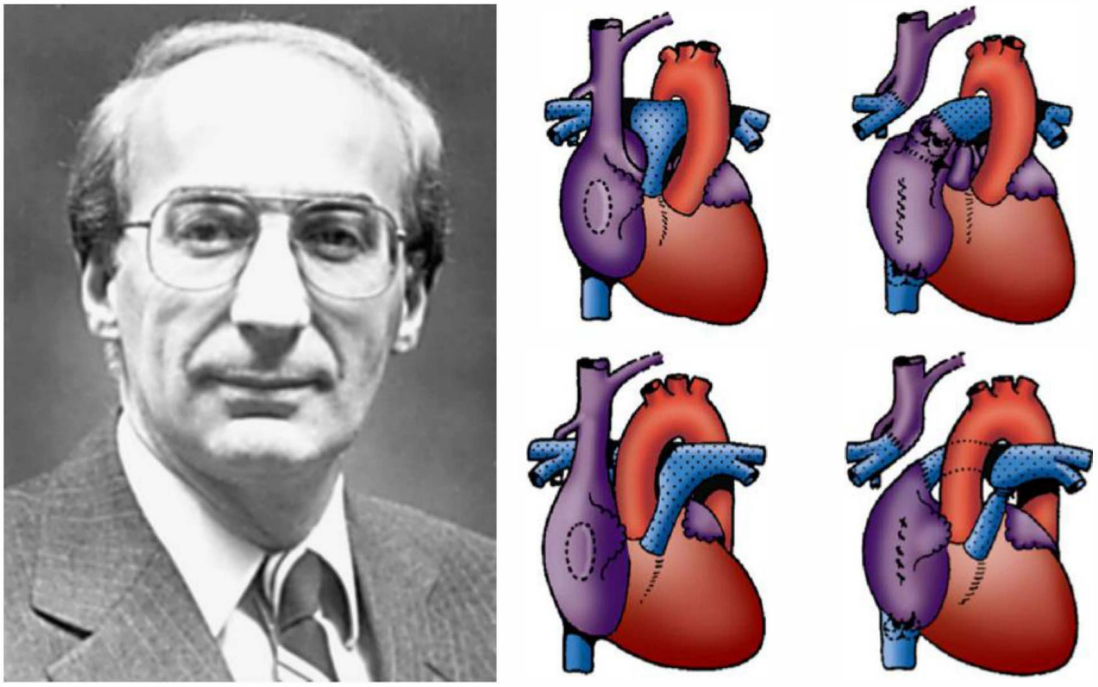


**FIGURE 58-6** Francois Maurice Fontan (left; reproduced from Westaby S. The foundation of cardiac surgery. *Landmarks in Cardiac Surgery*. Oxford, UK: Isis Medical Media Ltd, 1997:15). Right: Illustration from the original 1971 article detailing a novel surgical approach to tricuspid atresia and univentricular heart disease. (Reproduced from Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax* 1971;26:240.) Atriopulmonary connection with (upper panel) and without (lower panel) interposition of a valved homograft.

For children with malformations characterized by left-to-right shunting and pulmonary overcirculation, initial treatment of pulmonary hypertension by pulmonary arterial banding was first introduced by Muller and Dammann in 1952.[27] Although rarely utilized in biventricular hearts, pulmonary arterial banding still has a role in the initial staging of cardiac malformations characterized by univentricular morphology and pulmonary hyperperfusion (Chapter 77).

## EARLY CLOSED OR SEMICLOSED INTRACARDIAC OPERATIONS

The first attempts at closed intracardiac intervention were made to address pulmonic stenosis in cyanotic infants. T. Holmes Sellors of London reported the first successful transventricular pulmonary valvotomy in December 1946.[28] He had originally intended to perform a systemic-to-pulmonary shunt, but the chronic sequelae of tuberculosis made this initial plan unfeasible in his patient with Fallot's tetralogy. This approach was subsequently popularized by Lord Brock at Guy's Hospital and became the standard of care for pulmonic stenosis for much of the following decade. This procedure was later to be largely supplanted by open valvotomy on cardiopulmonary bypass and, eventually, by the much more often utilized percutaneous balloon valvotomy, first introduced in 1982 by Jean Kan at the Johns Hopkins Hospital.[29]

The initial growing success of palliative and closed procedures in prolonging the lives of patients affected by pathologies that would then, without intervention, have been unsurvivable[30] led to the development of several semiclosed procedures to address simple malformations (such as atrial septation defects) or to achieve initial palliation for more complex congenital anomalies.

Although an initial partially successful attempt at closure of an atrial septal defect (ASD) with the external suturing technique was described by Murray in 1948,[31] Robert Gross in 1952 reported the ingenious use of an "atrial well" to close ASDs.[32] The well was constructed by suturing a rubber funnel to the right atrial wall (Fig. 58-7), which made it possible to prevent exsanguination and air embolization. Through the well and under the stable and contained column of blood, the surgeon identified the defect by palpation and repaired it primarily without any direct visualization. Although the technique was by necessity quite rudimentary and imperfect, John Kirklin in 1956 reported a series of 29 patients undergoing successful ASD closure with the atrial well technique and without operative mortality.[33]

The "atrial well" could also be utilized to create an interatrial communication in patients with cyanotic lesions characterized by poor mixing. Atrial septectomy was nevertheless mainly performed in the era of semiclosed techniques with the method introduced by Blalock and Hanlon in 1948.[34] In this method, right-lung isolation was performed by temporarily occluding the right pulmonary artery and veins and by applying an appositely designed clamp (Fig. 58-8) to the groove of Sondergaard. The dorsal and right-lateral portion of the interatrial septum could then be excised and the interatrial groove closed primarily. These difficult operations[35,36] were eventually rendered obsolete by Rashkind's introduction of balloon septostomy in 1966.[37]

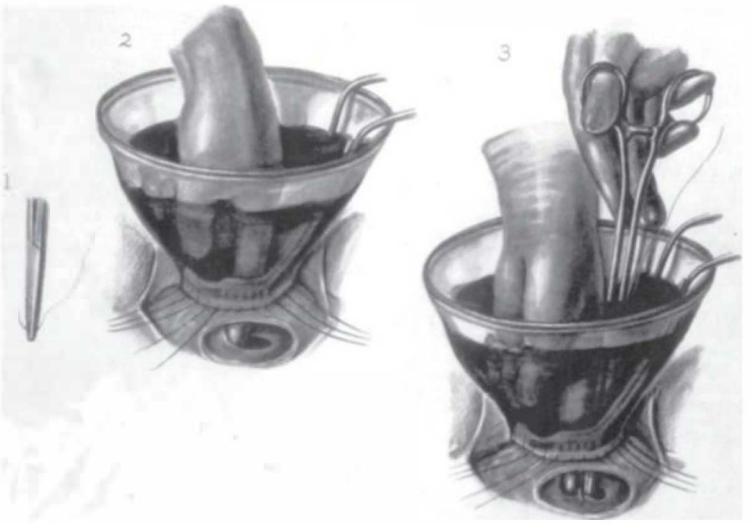



**FIGURE 58-7** The "atrial well" technique for closure of atrial septal defects, introduced by Robert E. Gross in 1952. A rubber cone is anastomosed to the convexity of the right atrium and the defect is palpated by the index finger of the operator under the column of blood (2). An appropriately loaded suture (1) is then utilized to close the defect (3). (From Westaby S. The foundation of cardiac surgery. *Landmarks in Cardiac Surgery.* Oxford, UK: Isis Medical Media Ltd, 1997: 400. With permission.)

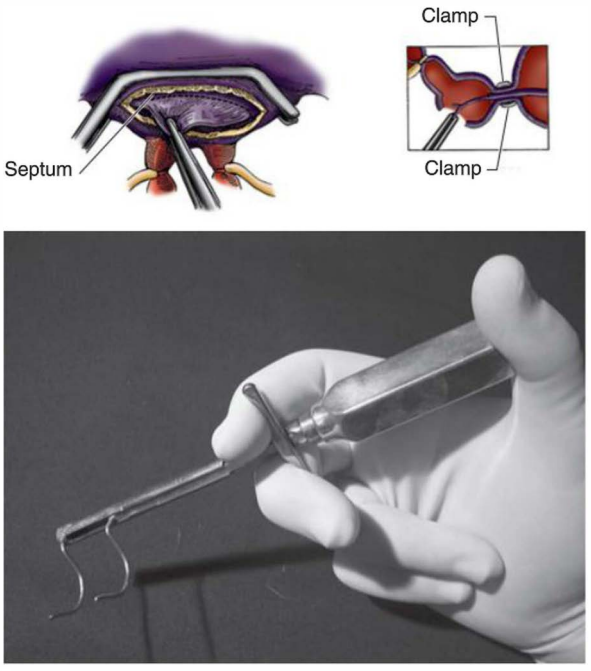



**FIGURE 58-8** Blalock-Hanlon atrial septectomy. Upper panel: Following isolation of the right pulmonary artery and veins, an incision is made in Sondergaard's groove (left) and the dorsal and leftward portion of the interatrial septum is excised (right). (Reprinted with permission from Waldhausen JA, Pierce WS. *Johnson's Surgery of the Chest*, 5th ed. Chicago: Yearbook Medical Publishers.) Lower panel: appositely designed clamp, utilized by Alfred Blalock to perform closed atrial septectomy. (Courtesy of Vivien Thomas, given t o the Division of Cardiac Surgery, The Johns Hopkins Hospital.)

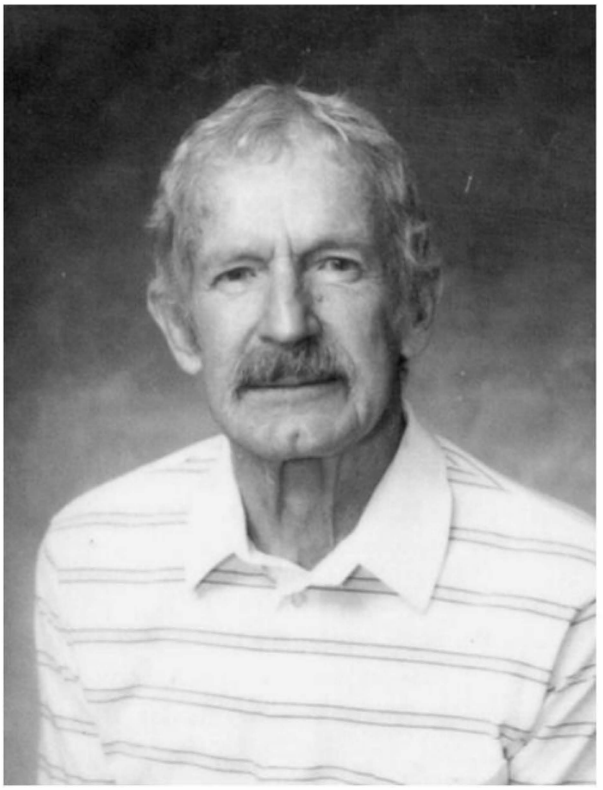


**FIGURE 58-9** Floyd John Lewis (1916–1993). (From Westaby S. The foundation of cardiac surgery. *Landmarks in Cardiac Surgery.* Oxford, UK: Isis Medical Media Ltd, 1997: 75. With permission.)

## INITIAL PHASE OF COMPLETE INTRACARDIAC REPAIRS

Closed or semiclosed operations failed to successfully address more complex morphologic problems, for which a true correction under direct vision was considered utopic until the early 1950s. The parallel investigation of hypothermia by the pioneering work of Wilfred Bigelow[38] and the introduction and development of extracorporeal circulation by John Gibbon, and the groups at the University of Minnesota and the Mayo Clinic made true intracardiac surgery a reality.

On September 2, 1952, John Lewis (Fig. 58-9) first achieved closure of an ASD under direct vision in a 5-year-old child at the University of Minnesota.[39,40] The procedure lasted 58 minutes and was preceded by a period of systemic surface cooling of 2 hours and 10 minutes. At a core temperature of 28°C, a right thoracotomy was performed and, during 5 minutes of inflow occlusion, the 2-cm ASD was primarily closed (Fig. 58-10). In merely a decade, the mortality for ASD closure was lowered from 30.2 percent (Gross's original series on ASD closure using the atrial well) to 12.1 percent (Lewis's inflow occlusion series).[41]

With the inflow occlusion technique, the time allowed for repair was below 10 minutes; to allow some degree of safety, the next natural evolution of intracardiac repair techniques was the introduction of extracorporeal circulation. John Gibbon was first to report successful direct closure of an ASD with the assistance of extracorporeal circulation in an 18-year-old patient at the University of Pennsylvania in 1953.[42]

Success and failure rapidly alternated in the early history of extracorporeal circuits. Two main techniques rapidly emerged: controlled cross-circulation and mechanical extracorporeal perfusion, championed by the University of Minnesota and the Mayo Clinic, respectively.

C. Walton Lillehei (Fig. 58-11) spearheaded the efforts to achieve intracardiac repair of complex cardiac lesions with the clinical introduction of controlled cross-circulation on March 26, 1954.[43] Lillehei, Varco, Cohen, and Warden pioneered this technique after extensive laboratory investigation in canines.[44,45] The first patient, a 1-year-old boy with an operative weight of 6.9 kg, was supported by his father (Figs. 58-12 and 58-13) for 19 minutes while the ventricular septal defect was closed primarily. The patient succumbed



**FIGURE 58-10** Intraoperative photograph from the first atrial septal defect closure performed by F. John Lewis on September 2, 1952. This is the first intraoperative picture of a patient with successful outcome after open-heart surgery.



**FIGURE 58-11** Clarence Walton Lillehei (1918–1999). (From Westaby S. The foundation of cardiac surgery. *Landmarks in Cardiac Surgery.* Oxford, UK: Isis Medical Media Ltd, 1997: 45. With permission.)

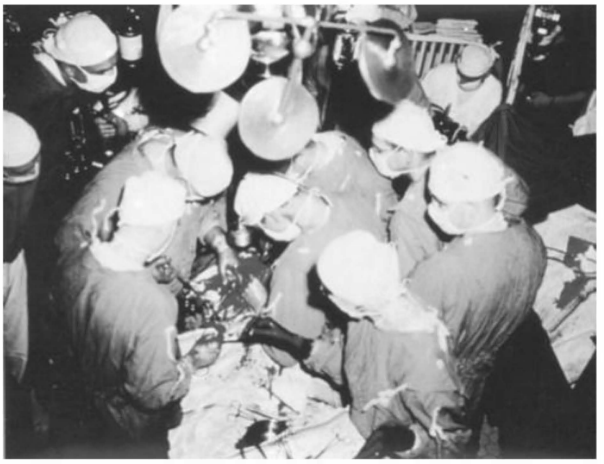


**FIGURE 58-12** University of Minnesota, Operating Room B, March 26, 1954: the first case of controlled cross-circulation. Dr. C. Walton Lillehei, to the right of the scrub nurse, is seen wearing a headlight. Opposite to Dr. Lillehei is Richard Varco. The patient's father is in the right background, and visible is the femoral donor cannulation site. Morley Cohen and Herbert Warden are seen behind Dr. Lillehei. Vincent Gott, the surgical intern on the cardiac service, is seen at the left upper corner of the picture, while assistant resident Norman Shumway is to his right. (Image courtesy of the University of Minnesota photographic archives.)

to pneumonia after 11 days, but this partial success did not undermine the morale of the surgeons at the University of Minnesota. Against institutional bias but with the support of Owen Wangensteen (Fig. 58-14), Lillehei, 2 weeks later, closed the ventricular septal defect of a 4-year-old girl, achieving long-term survival. Lillehei and coworkers performed a total of 45 operations with controlled cross-circulation. Among these was the first successful repair of tetralogy of Fallot, ventricular septal defect, and atrioventricular canal.[46–48] In this extraordinary series, operative mortality was 38 percent, and 79 percent of hospital survivors were alive at 30-year follow-up.[49] No operative deaths were directly attributable to extracorporeal perfusion, and postoperative heart block was most certainly implicated in several of the early failures. Because of this early, apparently insurmountable complication, Lillehei, Bakken, and coworkers also developed, from pressing necessity, the first temporary and, eventually, permanent implantable pacemakers.[50,51] By the end of the 1950s, the University of Minnesota turned to circulatory support with the DeWall-Lillehei oxygenator[52] and abandoned controlled cross-circulation.

John Kirklin (Fig. 58-15) at the Mayo Clinic concentrated all his efforts on cardiopulmonary bypass, developing the Mayo-Gibbon apparatus and its modifications.[53] In 1955, Kirklin reported a cohort of 38 patients with ventricular and other septation defects corrected with the aid of mechanical cardiopulmonary support.[54] This initial work established the relative safety of mechanical extracorporeal circulation

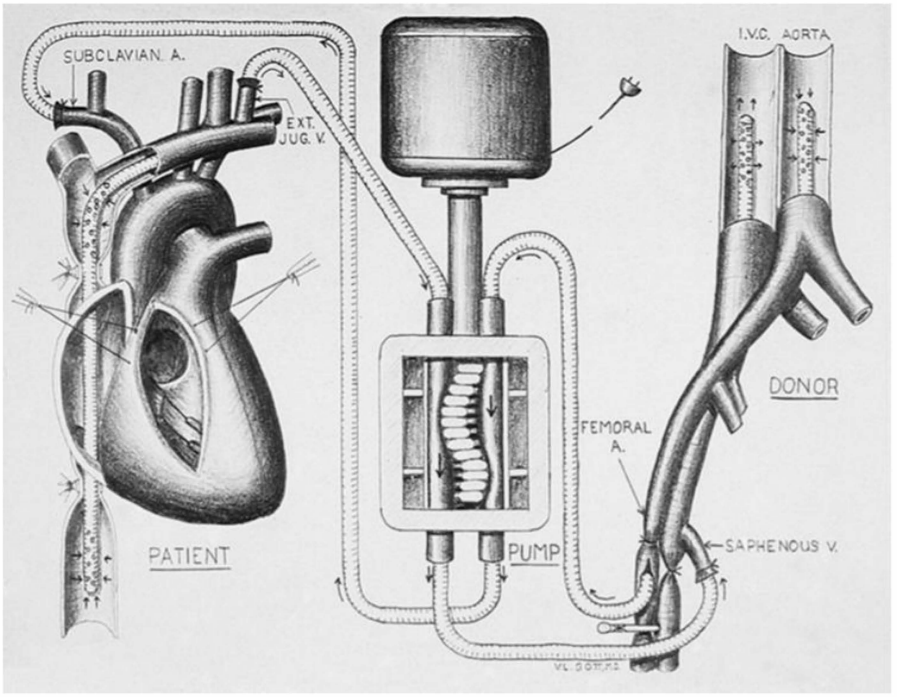



**FIGURE 58-13** Schematic illustration of the first case of controlled cross-circulation, 1954. Original drawing by the intern on C. Walton Lillehei's service, Vincent L. Gott.

and served as a platform for the development of the field of pediatric cardiac surgery. Utilizing the techniques developed in Minnesota, more complex anomalies could be successfully approached in the early 1960s without excessive mortality.[55–61]

In spite of this initial success, intracardiac repair remained as a daring undertaking in neonates and infants, largely because of the deleterious effects of cardiopulmonary bypass

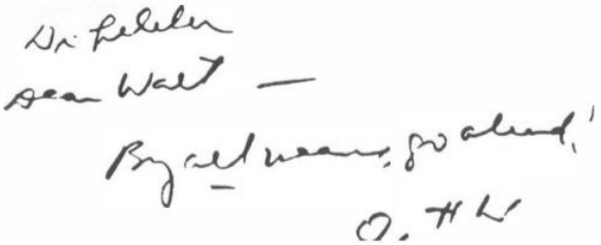


**FIGURE 58-14** Note from Owen H. Wangensteen written to C. Walton Lillehei on March 25, 1954, the eve of the first parental cross-circulation:
Dr. Lillehei
Dear Walt –
By all means, go ahead!
OHW
(From Lillehei CW. Section III: Cardiopulmonary bypass and myocardial protection. In: Stephenson LW, Ruggero R (eds). Heart Surgery Classics. Boston: Adams Publishing Group, 1994:126. With permission.)



**FIGURE 58-15** John Kirklin (1917–2004). (Courtesy of Dr. Joseph Dearani, Division of Cardiac Surgery, The Mayo Clinic. With permission.)

in children.[62] The size of the bypass circuits, the crudeness of the materials, and the underdevelopment of pediatric critical care made correction of cardiac anomalies in early infancy prohibitive. Between 1955 and the mid-1960s, smaller patients underwent correction almost exclusively following initial palliation by closed cardiac techniques.

## EXPANSION OF THE FIELD OF CONGENITAL CARDIAC SURGERY

Brian Barratt-Boyes was without doubt one of the most influential figures in the further advancement of congenital cardiac surgery. He returned to Green Lane Hospital (Auckland, New Zealand) after 2 seminal years at the Mayo Clinic (1953–1955). Sir Brian pioneered the concept of profound hypothermia and hypothermic circulatory arrest. This approach aggressively minimized the duration of exposure to extracorporeal surfaces and the subsequent inflammatory response, limiting it mainly to that needed for cooling and rewarming. The actual intracardiac repair could then be carried out expeditiously with no cannulae crowding an asanguinous field, thus greatly facilitating exposure in neonates and small infants. Furthermore, systemic cooling permitted relatively reliable myocardial protection before the routine introduction of cardioplegia[63–65]. This radical innovation allowed intracardiac repair of complex anomalies in neonates and infants, with excellent outcomes.[66,67] Of the 37 infants reported in his original 1971 article,[68] 33 had operative weight below 10 kg, and 25 patients were between 8 days and 12 months of age at the time of surgical correction. A gradual but steady shift toward early, complete one-stage intracardiac repair rather than initial palliation followed.[69–73] Complex anomalies such as total anomalous pulmonary venous connection, transposition of the great arteries,[72,73] complete atrioventricular canal,[74–76] and aortic arch anomalies[77,78] could be repaired in the neonatal period or in early infancy with much more acceptable morbidity and mortality as compared with the results of earlier corrective attempts.

This pioneering work was further developed by Castaneda (Fig. 58-16),[70–71] Jatene,[79,80] Norwood,[81,82] Bailey,[83,84] and others.[85–88] Thanks to the vision and determination of these contributors and to the exponential progress of perioperative care (Chapter 53),[37,89] the field had evolved over a mere 25-year period from treacherous attempts at palliation in older children to routine complete correction in neonates and infants.

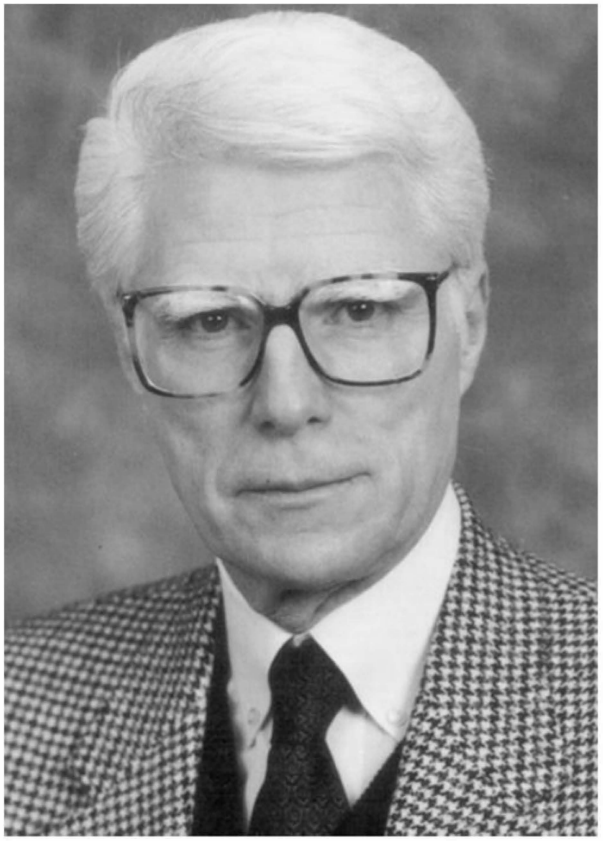


**FIGURE 58-16** Aldo Castaneda (1930– ). (From Westaby S. The foundation of cardiac surgery. *Landmarks in Cardiac Surgery*. Oxford, UK: Isis Medical Media, 1997:135. With permission.)

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# The Anatomy of Congenital Cardiac Malformations

*Robert H. Anderson*
*Andrew C. Cook*

## INTRODUCTION

The results of the surgical treatment of congenital cardiac malformations have been transformed within the last half-century. Prior to the development of cardiopulmonary bypass, it was impossible to even contemplate the repair of major malformations, even though ingenious surgeons had successfully closed simple intracardiac lesions such as holes between the atrial chambers. Even when it proved possible for the surgeon to work within the heart in the setting of a bloodless operative field, the results of operative repair were far from perfect, and many patients died subsequent to the operative procedure. Nowadays, it is unusual for any patient with a relatively simple defect to die, and even those with "complex" lesions are now expected to survive. There have been many reasons for these truly remarkable advances, but without question one has been the knowledge of detailed intracardiac anatomy accrued within recent decades. In the past, it was often thought that, in the setting of so-called complex malformations, this anatomy was difficult to understand. It is now recognized that, although the combination of given lesions can truly be complex, the anatomy itself is relatively straightforward provided that it is approached in straightforward fashion and using a system of analysis that is simple and logical. To achieve success, therefore, the pediatric cardiac surgeon must hone not only the surgical skills but also the intellectual rigor needed to analyze the structure of the congenitally malformed heart. It would be foolish to suggest that problems do not still exist in obtaining the necessary morphologic understanding, but these problems can be minimized by using a simple philosophy combined with use of words in their vernacular sense. Too many of the problems of the past have reflected linguistic rather than scientific disagreements. It remains appropriate to remember the aphorism attributed to Rudolf Virchow, namely that "those who fail to learn from the mistakes of the past are condemned to repeat them." In this chapter, therefore, we describe the basics of cardiac anatomy that permit the surgeon to diagnose and recognize the arrangement of the cardiac chambers during surgical procedures and at the same time appreciate the likely position of the vital conduction tissues. The concomitant advances made over recent years in diagnostic techniques are now such that the basic layout of the heart will have almost certainly been established prior to commencement of intracardiac procedures. Nonetheless, even in the most complex cases, preliminary diagnosis demands little more, in terms of morphology, than the distinction of a right atrium from a left atrium, a right ventricle from a left ventricle, and an aorta from a pulmonary trunk. It is such distinctions that provide the basis for simple sequential segmental analysis.[1] For the surgeon, the anatomy of holes and blockages within the heart and great vessels are of equal or even greater significance. This morphology is addressed elsewhere in the appropriate chapters of this book; therefore, we confine ourselves to showing how the anatomy of some important defects differs markedly from the normal arrangement. Our primary concern, however, is to establish the requirements for a systematic and simple approach to cardiac anatomy.

## APPROACHES TO THE HEART

The heart lies in the mediastinum. In most instances, it is found with its apex pointing to the left, and with about two-thirds of its bulk to the left of the midline. If not thus located, the surgeon should immediately consider the possibility that complex malformations lurk within the heart. When the heart is abnormally located, it is our preference to describe the arrangement in simple terms, such as "heart mostly in the right chest with the apex pointing to the left" or as appropriate. In this way, we avoid the need to define arcane terms, such as "pivotal dextrocardia" and comparable locutions. The surgeon usually approaches the heart through the midline anteriorly or via the thoracic cavities. Nowadays, a median sternotomy or a variation on this approach is used most frequently. It is fortunate for the surgeon that the area

of the mediastinum immediately behind the sternum is devoid of vital structures. Separate incisions can be made in the suprasternal notch and beneath the xiphoid process, the two being joined by blunt dissection. Splitting of the sternum exposes the pericardial sac lying between the pleural cavities. An important structure in this area is the thymus gland, particularly well developed in infants, which wraps itself over the pericardium in the area of the arterial pole. In dividing or excising the gland, the surgeon must take care of both the arterial supply, from the internal thoracic and inferior thyroid arteries, and the venous drainage through the thymic veins. The latter structures are fragile and often empty via a common trunk to the left brachiocephalic vein, which may be inadvertently damaged by undue traction.

Having exposed the pericardium, the surgeon should then remember that the vagus and phrenic nerves traverse its length, albeit well clear of the operative field (Fig. 59-1). The phrenic nerves, nonetheless, can be damaged should the pericardium be harvested for use as an intracardiac patch or baffle. Excessive traction on the pericardial cavity should be avoided, since it is easy to avulse the origin of the pericardiophrenic arteries, which accompany the phrenic nerves.

Lateral thoracotomies are made most frequently in the fourth intercostal space, using the posterior bloodless triangle between the edges of the latissimus dorsi, trapezius, and teres major muscles. An incision midway between the ribs avoids the intercostal neurovascular bundle, protected beneath the lower margin of the fourth rib. Such an incision takes the surgeon into the pleural space.

On the left side, posterior retraction of the lung exposes the middle mediastinum, revealing the left lobe of the thymus overlying the pericardium and the aortic arch, with its associated nerves and vessels. The aortic isthmus and descending aorta are readily approached in this fashion, dividing the parietal pleura posterior to the vagus nerve. Care must be taken to avoid the left recurrent laryngeal nerve, which takes its origin from the vagus and curves around the inferior border of the arterial ligament or, if this structure is still patent, the arterial duct (Fig. 59-2). The thoracic duct should also be avoided; this vessel drains at the junction of the left subclavian and internal jugular veins.

A right thoracotomy provides access to the right pulmonary artery and adjacent structures. On the right side, the right recurrent laryngeal nerve passes around the subclavian artery as it runs superiorly from the vagus toward the larynx. The stellate ganglion from the sympathetic trunk is also at potential danger in this region, inappropriate damage to this structure resulting in Horner syndrome.

## SURFACE ANATOMY OF THE HEART

The nature of the cardiac chambers is readily determined by external inspection. The morphology of the appendages best distinguishes the right from the left atrium. These outpouchings usually clasp the arterial pedicle, with one appendage to each side (Fig. 59-3). The arrangement in which both appendages are on the same side of the pedicle

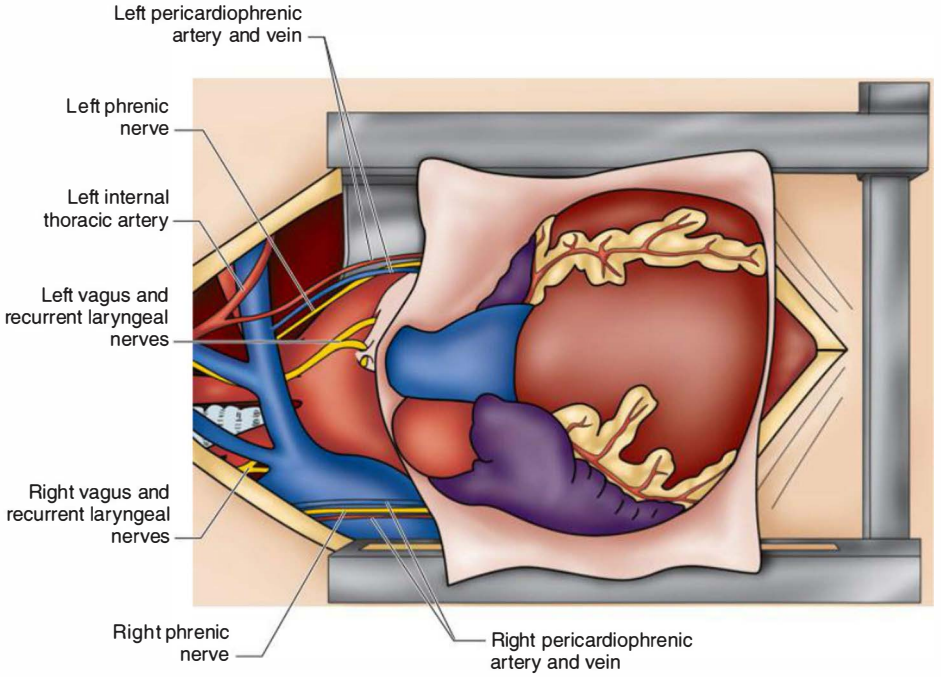



**FIGURE 59-1** The diagram shows the relationships between the vagus and phrenic nerves and the heart contained within its pericardial sac as seen by the surgeon approaching the heart through a median sternotomy.

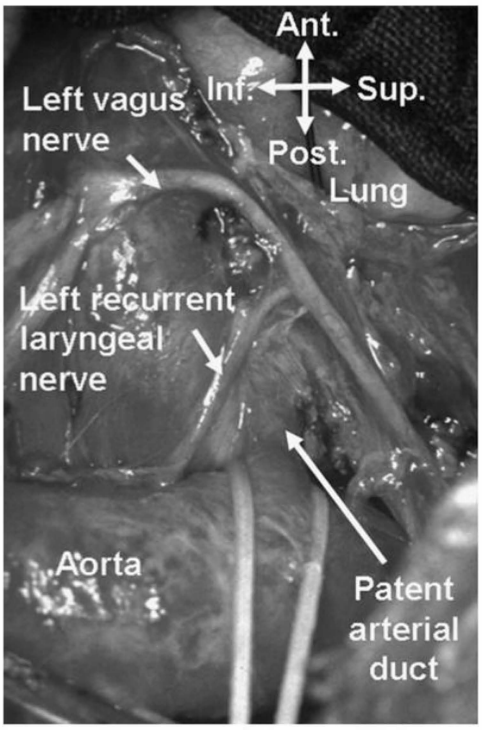



**FIGURE 59-2** This operative view through a left thoracotomy shows the relationships of the recurrent laryngeal nerve relative to the arterial duct. (Courtesy of Benson Wilcox, MD, with permission.)

is called juxtaposition of the atrial appendages. Should the two appendages both be left-sided, then the cardiac chambers and arterial trunks are almost always abnormally joined together. If both appendages are to the right, however, this being a much rarer finding, the heart is again likely to be malformed, but in much simpler fashion, sometimes with no more that an atrial septal defect. Juxtaposition of the appendages also distorts the internal atrial architecture, particularly the atrial septum—a situation that can produce problems unless properly recognized.

In this chapter, we use the terms "right" and "left" to indicate morphology rather than position, this being one of the basic rules of congenital cardiac morphology. If position is also abnormal, this should be described separately. The appendages are the best structures with which to distinguish the morphologically right and left atriums. The right appendage has an obviously triangular shape, in contrast to the tubular left appendage. Shape, however, can be modified by abnormal hemodynamics. In situations of uncertainty therefore, the surgeon should examine carefully the junctions between the appendages and the remainder of the atrial chambers.[2] The essential feature of the right atrium is that the pectinate muscles extend all around the atrioventricular junction to the back of the heart. In the left atrium, in contrast, the posterior wall is entirely smooth, the pectinate muscles being confined within the tubular appendage. When the triangular appendage is right-sided and the tubular appendage left-sided, this usual arrangement is frequently called "situs solitus." Our preference, as already stated, is to use words which have currency in normal language, so we prefer simply to describe it as "the usual arrangement." On rare occasion, the tubular appendage will be right-sided, with the triangular one on the left side. This is best described as "the mirror-image arrangement." Although often called "situs inversus," the appendages in this setting are truly mirror-imaged rather than being turned upside down. Mirror imagery is rare. In the setting of complex malformations, it is more frequent to find the arrangements in which both the appendages have comparable morphology. Both appendages can then be either broad and triangular, with pectinate muscles extending all around the atrioventricular vestibules, or

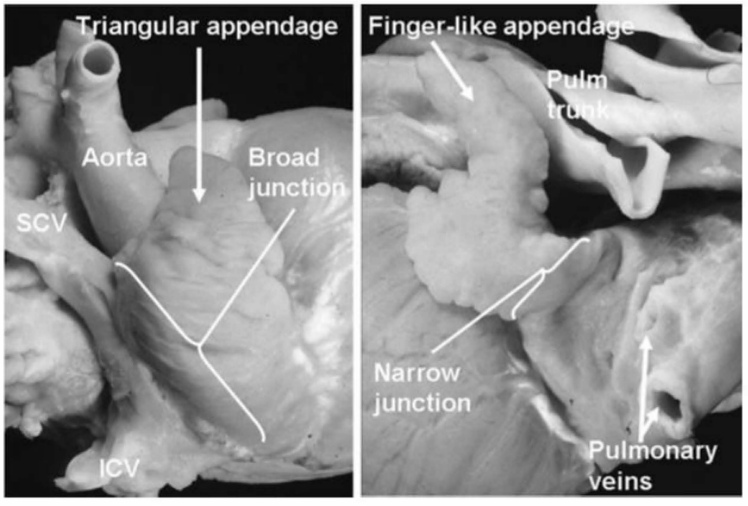



**FIGURE 59-3** These lateral views of the heart, taken in anatomic position, show the different shapes of the right and left atrial appendages.

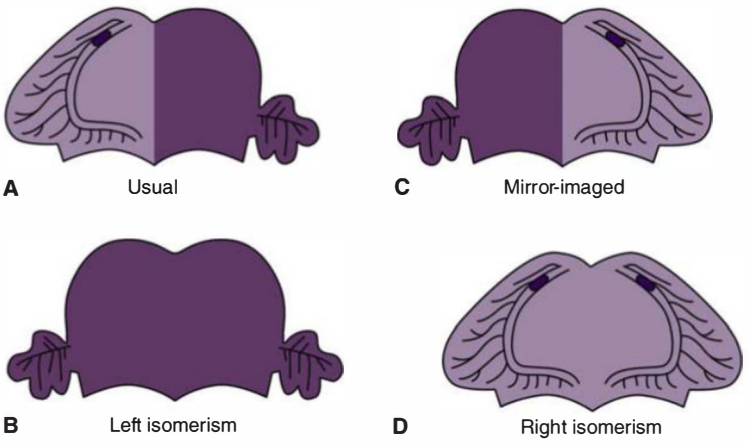



**FIGURE 59-4** The potential arrangement of the atrial appendages. Note the location of the sinus node (hatched commas or dots; see text for further discussion).

else both can be tubular and narrow, with smooth posterior atrial walls on both sides (Fig. 59-4). These arrangements are accurately described as isomerism of the right or left atrial appendages, respectively. Patients with such arrangements of the appendages also typically have malposed abdominal organs, along with an isomeric arrangement of the lungs and bronchial tree.[1,2] The overall arrangement is called visceral heterotaxy and, in the past, was often categorized on the basis of splenic morphology. These syndromes are the harbingers of the most complex combinations of intracardiac lesions, but it is now unusual for such patients to be denied attempted surgical correction. By the simple expedient of inspecting the appendages, the surgeon now has the means of diagnosing these entities directly in the operating room, should the conditions not have been recognized during the diagnostic workup. Indeed, recognition of the appendages is the more important to the surgeon, since sometimes there is discordance between splenic anatomy and the arrangement of the appendages.[3] It is accurate recognition of the appendages that guides the surgeon to an appreciation of the likely location of the sinus node.[4]

Thus, the surgeon should examine carefully the junctions between the appendages and the atrial venous components. If the junction is morphologically right, there will be an extensive terminal groove, marking the site of the terminal crest internally (Fig. 59-5). The sinus node is always located in the immediately subendocardial position within this groove, positioned lateral to the crest of the atrial appendage (Fig. 59-6). The morphologically left junction is never marked by any such prominent groove and similarly lacks a sinus node. Should both junctions be morphologically right, the sinus node will be duplicated and the surgeon should respect both junctions. In the setting of isomeric left appendages, in contrast, the sinus node will be hypoplastic or even absent, and the surgeon should be aware that the nodal remnant can be positioned in the smooth atrial wall close to the atrioventricular junctions.[4]

Having inspected the appendages, the surgeon should turn attention to the venoatrial connections, ensuring that all the pulmonary veins, along with the caval veins and the coronary sinus, are in their appropriate positions. Search should always be made for a persistent left superior caval vein. This will be found between the left appendage and the left pulmonary veins. If the surgeon has already established that there is isomerism of the left atrial appendages, then attention should be directed to the inferior caval vein, which is often interrupted in this setting, venous flow from the abdomen being returned through the azygos venous system, which will be correspondingly enlarged.

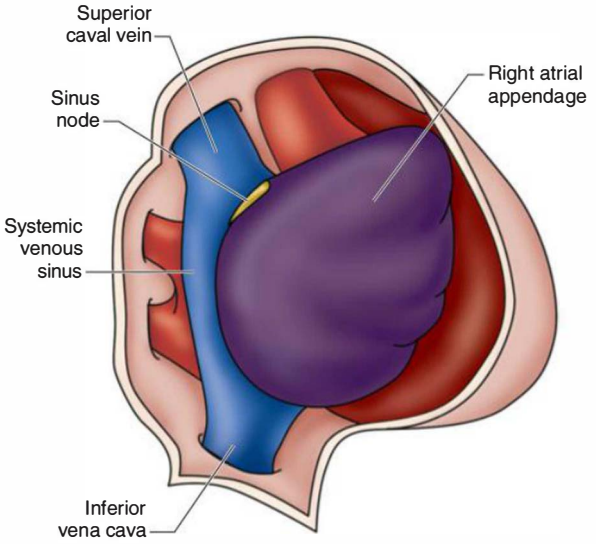



**FIGURE 59-5** The drawing shows how the terminal groove interposes between the right atrial appendage and the systemic venous component. The heart is shown in anatomic orientation, with the subepicardial position of the sinus node marked.

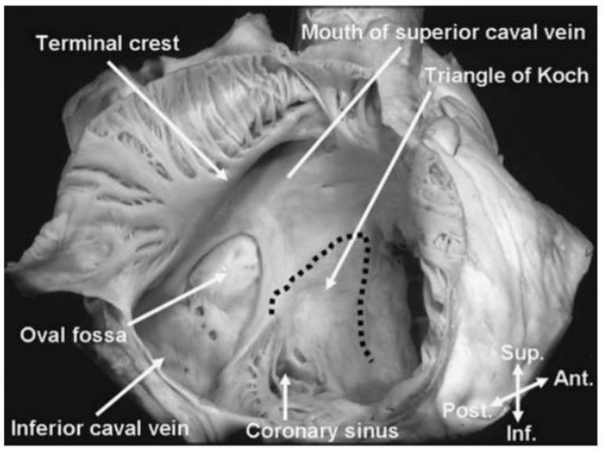



**FIGURE 59-6** The right atrium has been opened with the heart in anatomic position to show the terminal crest and the location of the triangle of Koch. Note the apparent extensive area occupied by the septal surface.

External inspection also provides significant information concerning the structure of the ventricular mass. It is the positions of the interventricular branches of the coronary arteries that are the guide.[5] In the usual situation, the anterior interventricular coronary artery is a branch of the main stem of the left coronary artery, descending close to the obtuse margin of the ventricular mass. Should this artery take its origin from a coronary artery arising in right-sided position from the aortic root, the aorta itself being anterior to the pulmonary trunk, then almost always the ventricles themselves will be arranged in mirror-imaged fashion (so-called left-hand ventricular topology) with the morphologically left ventricle then positioned on the right. Identification of such a coronary arterial pattern should alert the surgeon to the likely presence of congenitally corrected transposition, the combination of discordant atrioventricular and ventriculoarterial connections (see below). Equally obvious should be the arrangement in which two arteries of comparable size take origin from an anteriorly positioned aorta, delimiting the position of a small ventricle on the anterior surface of the ventricular mass. Such a finding is indicative of disproportion between the sizes of the ventricles. The most frequent disproportion is seen when the left ventricle is dominant and the right ventricle is small, as in double-inlet left ventricle or tricuspid atresia. Should prominent interventricular arteries not be evident on the anterior ventricular surface, suspicion should be raised that there is a solitary ventricle of indeterminate morphology. This pattern, however, is exceedingly rare. Much more frequently in this setting, the right ventricle will be dominant, with the small left ventricle hidden on the diaphragmatic surface of the ventricular mass. This is the typical pattern seen in hypoplasia of the left heart.

In examining the ventricular mass, note should also be taken of the relationship of the arterial trunks, confirming first that there are separate aortic and pulmonary trunks as opposed to a common or solitary trunk. There will usually be separate trunks, and typically the aortic trunk is then posterior- and right-sided, with the pulmonary trunk spiraling around the aorta as it divides into right and left pulmonary arteries. This is the "normal relationship."

Abnormal relationships of the great arterial trunks are indicative of intracardiac malformations, albeit that the positions and connections of the cardiac chambers themselves cannot be inferred from such knowledge. Abnormal arterial positions, nonetheless, give important clues to the presence of particular lesions, which nowadays will almost certainly have been accurately diagnosed before the patient reaches the operating room. An anterior and right-sided aorta is the typical feature of discordant ventriculoarterial connections, usually known as "transposition," but is also seen when both arterial trunks arise from the right ventricle. When the aorta is anterior and left-sided, most frequently the transposition will be congenitally corrected as discussed above, but this pattern can also be seen with double outlet from the right ventricle. The aorta can also be anterior and left sided when the connections are concordant across both the atrioventricular and ventriculoarterial junctions, a rare situation sometimes called "anatomically corrected malposition."[6] A left-sided and anterior aorta can also be found with regular transposition. All this variation serves to emphasize that relationships of the arterial trunks are at best a guide to the specific connections of the cardiac segments.

## ANATOMY OF THE CARDIAC CHAMBERS

The perceptive reader will have ascertained from our descriptions thus far that one of the major features of the congenitally malformed heart is that the cardiac chambers are not always in their usual position, nor are they joined as expected to their neighbors. The most important rule of congenital cardiac anatomy, nonetheless, is that each chamber has a relatively constant anatomy irrespective of its position or its connections, albeit that a subtle change in morphology is found when the chambers are connected in abnormal fashion or when the junctions between the cardiac segments are themselves malformed. In this section, therefore, we concentrate our attention on the expected normal morphology, emphasizing when the surgeon should expect to find abnormal arrangements.

### The Right Atrium

As already discussed, the most distinctive feature of the right atrium is its extensive triangular appendage, which is separated from the venous component of the atrium by the terminal groove (Fig. 59-5). When viewed by the surgeon, the superior caval vein enters the left-hand side of the venous component, with the inferior caval vein to the right-hand side. The venous component itself is then seen by the surgeon as a sleeve, being separated inferiorly from the right pulmonary veins by the extensive interatrial groove. This

groove, also known as Waterston's or Sondergaard's groove, is a deep infolding between the right and left atrial walls.

Opening of the right atrium reveals the extensive terminal crest (Fig. 59-6). This muscular bundle underlies the terminal groove, encasing the orifices of both the superior and inferior caval veins, and extending anteriorly toward the atrial septum. In the region of the septum, it becomes a muscular ridge, the eustachian ridge, which separates the orifice of the inferior caval vein from the mouth of the coronary sinus. The mouths of these venous structures are often guarded by sickle-shaped fibrous folds of varying dimensions, the eustachian and thebesian valves. The fibrous commissure of these two valves buries itself in the musculature between the coronary sinus and the oval fossa; as viewed by the surgeon, it runs toward the left-hand margin of the tricuspid vestibule. This important structure, the tendon of Todaro, forms one boundary of the crucial triangle of Koch (Fig. 59-6). When seen in the operating room, the tendon forms the most distant border of the triangle, while the site of annular attachment of the septal leaflet of the tricuspid valve is closer to the surgeon. The atrioventricular node is found at the apex of this triangle, with the atrioventricular bundle penetrating from the apex to pass into the left ventricular outflow tract.

When the right atrium is viewed as shown in Figure 59-6, the impression is gained of an extensive septal surface between the right and left atriums. Sectioning shows that this is not the case (Fig. 59-7). The atrial septum, defined as the tissue that can be removed without encroaching on the pericardial cavity,[7] is confined to the floor of the oval fossa and its anteroinferior margins.[7,8] The left-hand side of the fossa, as viewed by the surgeon, is the atrial wall overlying the aortic root. The septum secundum, between the fossa and the orifice of the superior caval vein, positioned superiorly with the heart in anatomic location but seen as an inferior structure by the surgeon, is no more than the deeply infolded walls of the interatrial groove.

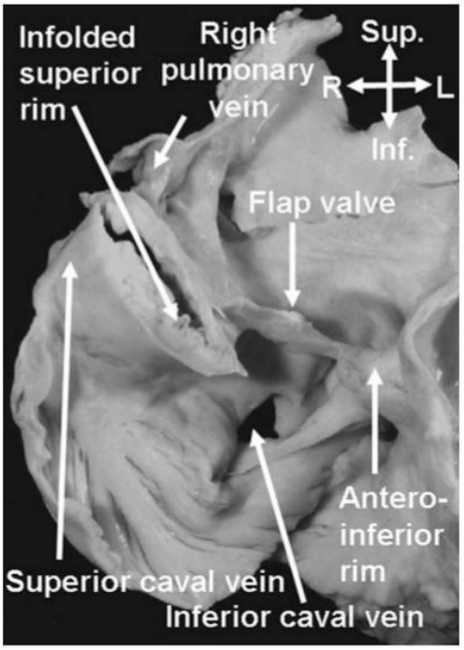



**FIGURE 59-7** Sectioning of the heart reveals that only the oval fossa and its inferoanterior rim are true septal structures. The other borders are infoldings of the atrial walls.

## The Left Atrium

Overall, the left atrium (Fig. 59-8) has a much simpler structure than the right atrium but also possesses an extensive body, which is lacking in the right atrium. The appendage accounts for less of the chamber than on the right side. The venous component, located posteriorly and superiorly, receives the four pulmonary veins, one at each corner. When seen by the surgeon entering through the atrial roof, the narrow opening of the tubular appendage is to the left hand, while the septal surface is to the right. The smooth inferior and posterior margin of the mitral vestibule overlies the coronary sinus as it runs round from the obtuse margin of the ventricular mass. The septal surface of the left atrium is much simpler than that of the right, being formed by the flap valve of the oval fossa (Fig. 59-8).

## The Atrioventricular and Ventriculoarterial Junctions

Knowledge of the structure of the junctions between the cardiac components is fundamental to the proper understanding of several congenital anomalies, particularly

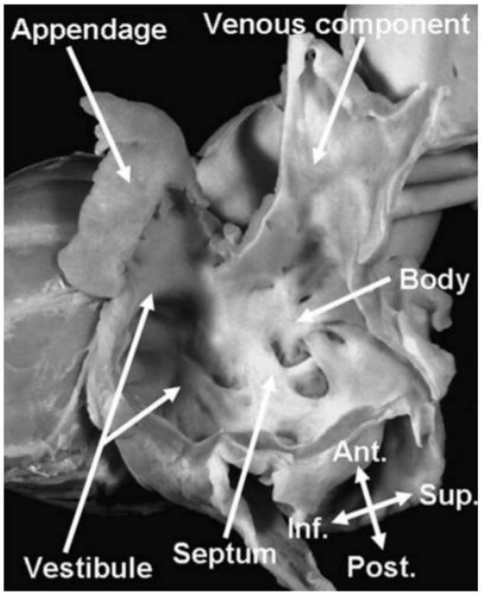



**FIGURE 59-8** The components of the left atrium are shown in anatomic orientation as seen in left lateral position.

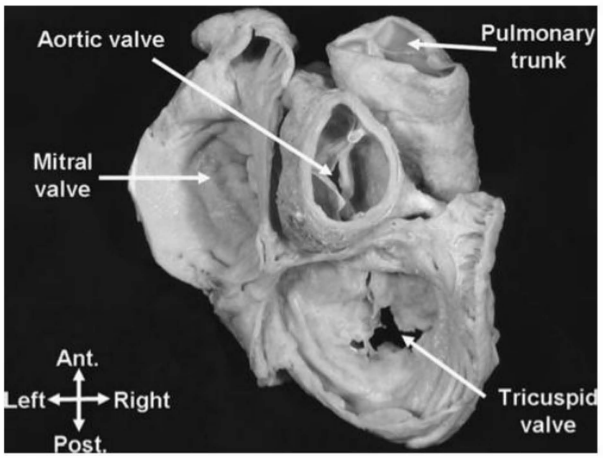



**FIGURE 59-9** The atrial myocardium has been removed from the base of the heart, which is photographed from above and from the right to show the arrangement of the atrioventricular junctions relative to the ventriculoarterial junctions.

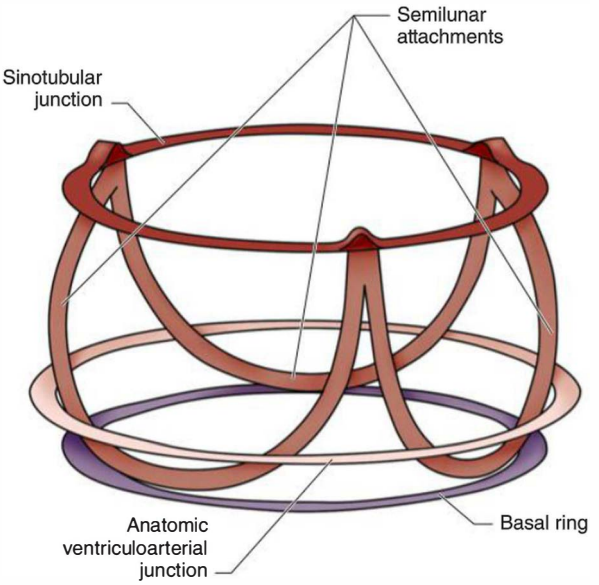



**FIGURE 59-10** The drawing shows how the arterial roots are formed in the style of a coronet, with the semilunar attachments of the valvar leaflets crossing the anatomic ventriculoarterial junction. The basal ring is a virtual ring, made by joining together the basal attachments of the leaflets. The sinotubular junction, in contrast, is a true annular structure and marks the distal boundary of the arterial root.

atrioventricular septal defects in the setting of common atrioventricular junctions.[9] The salient anatomy of both these junctions, and the relationship between the valves guarding them, is well seen when the musculature of the atrial chambers and the arterial trunks is dissected away from the ventricular base, which can then be viewed from its superior aspect (Fig. 59-9). Although each of the four cardiac valves is usually described as possessing an annulus, in reality none has a true and complete fibrous ring supporting its leaflets. It is the mitral annulus that approximates most closely to the concept of a ring, albeit that it is more akin to an oval saddle, and parietally there is often very little collagenous tissue supporting the mural leaflet of the valve. In the tricuspid orifice, it is very rare to find a collagenous annulus. Instead, it is the fibro fatty tissues of the atrioventricular groove that separate the atrial muscle from the ventricular mass. In the case of the arterial valves, the concept of a "ring" is totally deficient. For both the aortic and pulmonary valves, each of the three leaflets is attached to the underlying ventricular structures in semilunar fashion. Although encased in a circular tube, the attachments of the arterial valvar leaflets, when considered as a whole, take the form of a coronet, with the hinge lines of the leaflets tenting up to reach the sinotubular junction and sweeping down to the nadir of the attachments at the ventricular bases (Fig. 59-10).[16] In the right ventricle, these basal attachments are exclusively supported by ventricular muscle, specifically by the free-standing subpulmonary infundibulum. For the aortic valve, in contrast, a good half of the valvar circumference is supported by fibrous and collagenous tissues. This is because the leaflets of the aortic valve usually have extensive fibrous continuity with those of the mitral valve and, via the membranous septum, also with the leaflets of the tricuspid valve (Fig. 59-11). The two ends of the region of aortio-mitral valvar continuity are thickened to form the right and left fibrous trigones, with the right trigone itself forming an integral part of the fibrous mass where the aortic root is continuous with the leaflets of the tricuspid valve (Fig. 59-12). This whole area is called the central fibrous body, incorporating the so-called membranous septum, which forms the medial wall of the subaortic outflow tract beneath the zone of apposition between the right coronary and noncoronary leaflets of the aortic valve.

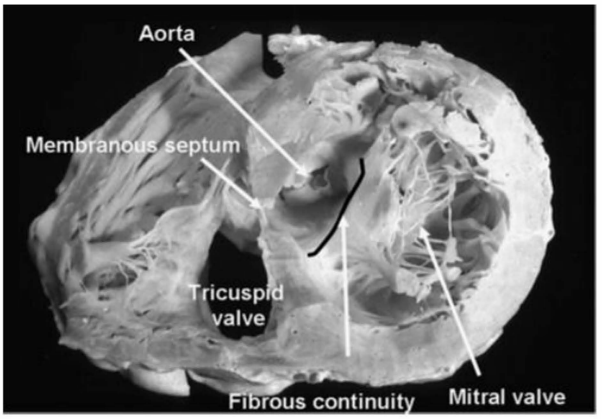



**FIGURE 59-11** The short axis of the ventricular mass is photographed from beneath in left anterior oblique orientation, showing the relationship between the leaflets of the aortic and mitral valves. Note also the fibrous continuity with the tricuspid valve through the substance of the membranous septum.

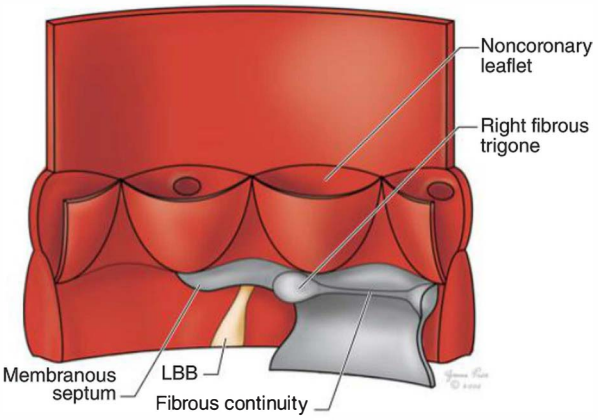



**FIGURE 59-12** The drawing shows how the right trigone and the membranous septum form the so-called central fibrous body.

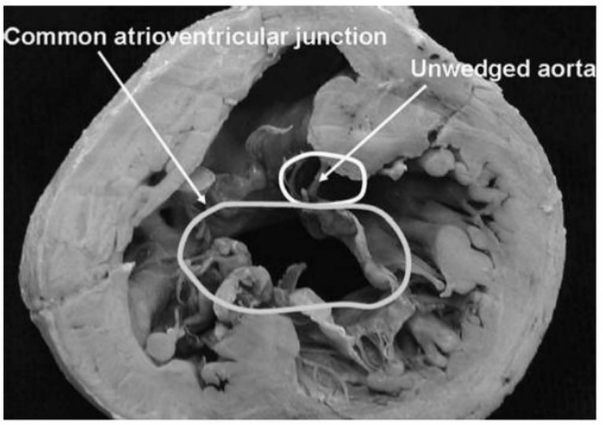



**FIGURE 59-13** An atrioventricular septal defect with the common atrioventricular junction has been sectioned in the short axis of the ventricular mass and photographed from beneath (compare with Fig. 59-11). The essence of the lesion is the common atrioventricular junction.

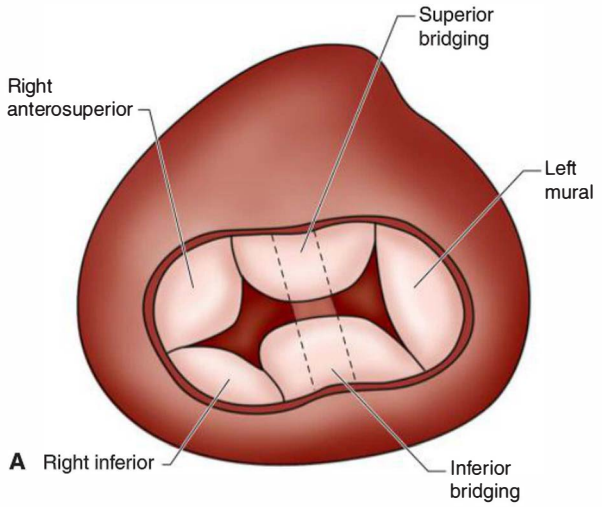
The attachment of the septal leaflet of the tricuspid valve divides this membranous septum into its atrioventricular and interventricular components.

Viewing the atrioventricular junctions from their ventricular aspect (Fig. 59-11) shows how the subaortic outflow tract "lifts" the aortic leaflet of the mitral valve away from the muscular ventricular septum. Because of this, the two atrioventricular valves are attached to opposite sides of the septum over a remarkably short distance. In this short area, the tricuspid valve is attached to the septum more toward the ventricular apex than is the mitral valve, producing the well-recognized echocardiographic feature of valvar off setting. In times gone by, we considered this area to be the "atrioventricular muscular septum."[9] We now know that, in this area, an extension of the inferior atrioventricular groove interposes between the atrial and ventricular musculatures. The area is better likened to a sandwich rather than a septum.[10] It is into the atrial aspect of the sandwich that the coronary sinus opens to the right atrium, having traversed the posterior and inferior aspect of the left atrioventricular junction. The atrial components of the "atrioventricular muscular sandwich" contain the atrioventricular node, which lies on the sloping atrial aspect of the junction. From this position, the atrioventricular bundle is able to penetrate the central fibrous body and reach the crest of the muscular ventricular septum in the left ventricular outflow tract. The surgical landmark to this point of penetration is the zone of apposition between the right and noncoronary aortic valvar leaflets. As seen from the right atrium, it is the landmarks of the triangle of Koch that delineate the site of the specialized atrioventricular conduction tissues. Seen from the left atrium, the septal end of the zone of apposition between the leaflets of the mitral valve demarcates the area of danger. In approaching from the right ventricle, so as to protect the conduction tissue, the surgeon must avoid the area immediately adjacent to the medial papillary muscle and the zone of apposition between the septal and anterosuperior leaflets of the tricuspid valve.

It is the atrioventricular muscular sandwich together with the atrioventricular component of the membranous septum that are lacking in the group of lesions known as atrioventricular canal malformations, or more recently as atrioventricular septal defects.[9] Attention to the junctional morphology of these lesions shows that the phenotypic feature is a common atrioventricular junction (Fig. 59-13). The valve guarding the common junction closes in the fashion of a pentafoliate structure, irrespective of whether there is a common valvar orifice, or separate orifices for the right and left ventricles, the latter morphology being the phenotypic feature of the so-called ostium primum defect.[9] Attention to the pattern of closure of the left ventricular component of this common valve shows that it possesses three leaflets, one being exclusive to the left ventricle and the other two being the left ventricular components of leaflets that bridge the ventricular septum (Fig. 59-14). Analysis in this fashion shows that the "cleft" in the left atrioventricular valve, a source of appreciable confusion over the years, is no more than the zone of apposition between the left ventricular components of these two leaflets bridging the ventricular septum.

## The Right Ventricle

Traditionally, it has been customary to divide ventricles into sinus and conus. This convention is adequate for the normal heart, although less than ideal. In our opinion, it is better to consider ventricles as possessing three rather than two components, namely, the inlet, apical trabecular, and outlet portions (Fig. 59-15). All ventricles, no matter how deformed, are readily described using this tripartite convention. For instance, the small ventricles in functionally univentricular hearts with a dominant left ventricle, whether produced by double-inlet- or tricuspid atresia, possess apical trabecular and outlet components. As such they are logically described as ventricles, and



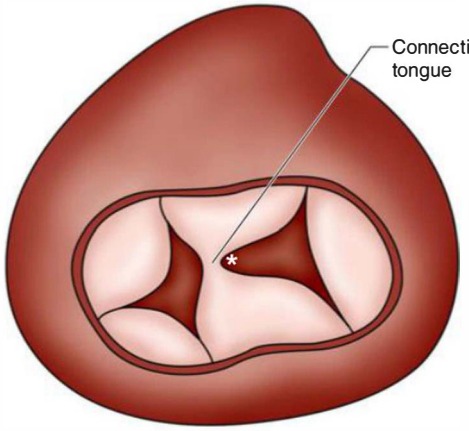
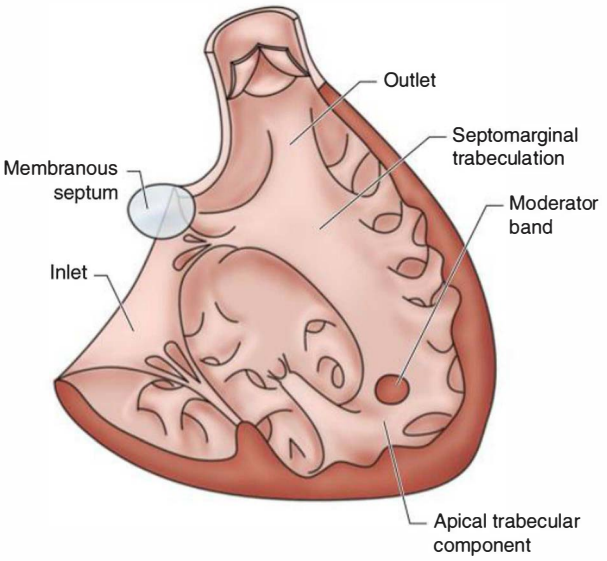




**FIGURE 59-14** The drawing shows the arrangement of the leaflets of the common valve that guards the common atrioventricular junction, as shown in Figure 59-13, when (**A**) there is a common atrioventricular junction and (**B**) there are separate valvar orifices for the right and left ventricles. Note that the left atrioventricular valve possesses three leaflets and that the so-called cleft (asterisk) is the zone of apposition between the left ventricular components of the leaflets, which bridge the ventricular septum.



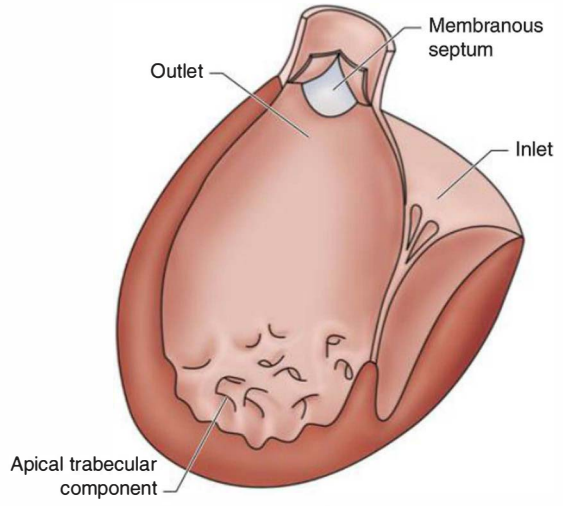




**FIGURE 59-15** The drawing shows how both right and left ventricles can be described as possessing inlet, apical trabecular, and outlet components.

the hole between them and the dominant left ventricle appropriately described as a ventricular septal defect.[11]

In describing the atrioventricular valves, integral components of most ventricles, we must be able to distinguish their leaflets. This is best done by viewing the valves in their closed rather than open positions. It is then an easy matter to recognize the number of zones of apposition within the components of the skirt of leaflet tissue. Such an approach is much better than taking the "commissural cords" as the criterion of division between leaflets. In using the criterion of commissural cords, it is difficult to determine whether the mitral valve has two or four leaflets.[12] When viewed from the stance of the closed valve, there is no question but that the mitral valve possesses two leaflets with a solitary zone of apposition between them.[13] In similar fashion, viewing the closed tricuspid valve shows that it truly possesses three leaflets.[14] And, when seen in attitudinally appropriate orientation, these leaflets are located septally, anterosuperiorly, and inferiorly within the valvar orifice.

The right ventricle, when normally constituted, possesses the tricuspid valve in its inlet portion. The zone of apposition between its septal and anterosuperior leaflets, supported by the medial papillary muscle, is intimately related to the site of penetration of the atrioventricular bundle. The feature of the apical trabecular component is its typically coarse

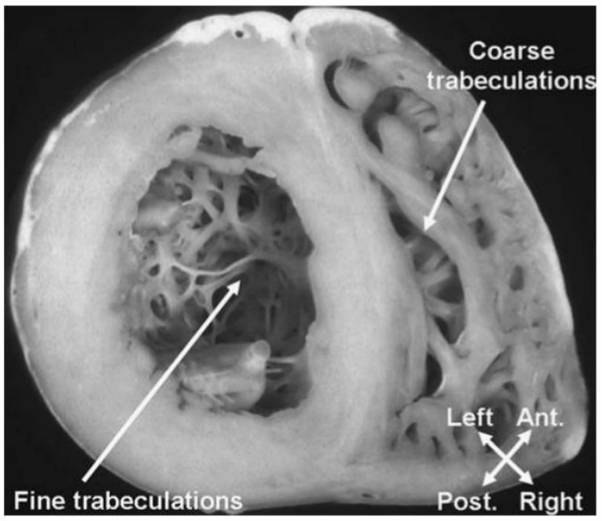



**FIGURE 59-16** The view of the apical part of the ventricular mass, seen from above, shows the difference in apical trabeculations between the right and left ventricles.

trabeculations. Indeed, it is on this basis that the ventricle is most reliably differentiated from the finely trabeculated left ventricle (Fig. 59-16).

In the normal right ventricle, the outlet component is a free-standing muscular sleeve, the infundibulum (Fig. 59-17). The apparently "septal" aspect of this infundibulum is part of the supraventricular crest, which interposes between the attachments of the leaflets of the tricuspid and pulmonary valves. Dissection shows that this structure is no more than the parietal wall of the heart, its removal emphasizing the important relationship to the right coronary artery

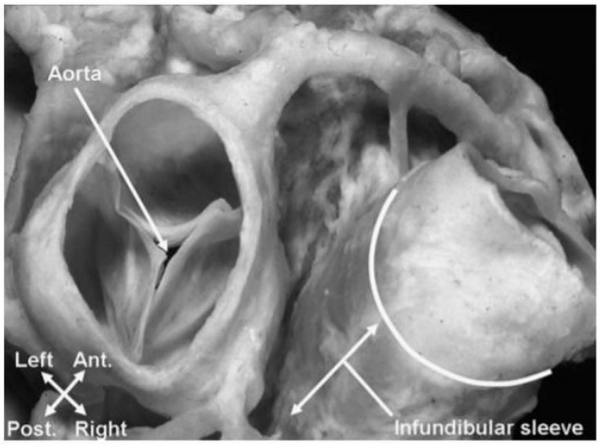



**FIGURE 59-17** The free-standing muscular infundibulum of the right ventricle has been swung away from the aortic root, showing the deep tissue plane that separates the two arterial roots. The white line shows the circular junction between the infundibular musculature of the right ventricle and the wall of the pulmonary trunk.

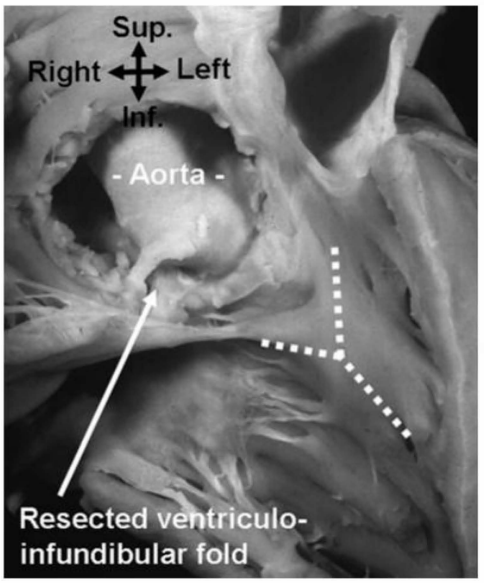



**FIGURE 59-18** The larger part of the supraventricular crest has been cut away, showing that it is no more than a fold in the parietal ventricular wall. Note the aorta giving rise to the right coronary artery. The dissection also shows how the crest inserts between the limbs of the septomarginal trabeculation (Y-dotted lines). This extensive trabeculation extends to the apex of the right ventricle, with multiple septoparietal trabeculations taking origin from its anterior aspect.

(Fig. 59-18). The crest inserts between the limbs of the extensive septal muscle bundle, which runs down into the apical trabecular component, splitting into various trabeculations including the moderator band, the anterior papillary muscle, and various septoparietal trabeculations (Fig. 59-18). In the past, this extensive bundle was often viewed as part of the supraventricular crest, and it still retains the designation of "septal band." Logic dictates that this structure cannot, at the same time, be both septal and supraventricular. It is better to distinguish this important structure as the septomarginal trabeculation, separating it in this way from both the ventriculoinfundibular fold, which forms the supraventricular crest, and the outlet component of the ventricular septum.[15] In the normal heart, however, it is not possible to distinguish with certainty that small part of the muscular septum between the subaortic and subpulmonary outlets. This part of the septum is better seen when the ventricular septum itself is deficient and is most obvious when both arterial trunks take their origin predominantly or completely from the right ventricle, as in tetralogy of Fallot (Fig. 59-19A) or double-outlet right ventricle (Fig. 59-19B).

## The Left Ventricle

As with the right ventricle, we find it best to analyze the left ventricle as possessing inlet, apical trabecular, and outlet components (Fig. 59-13). The inlet component contains the

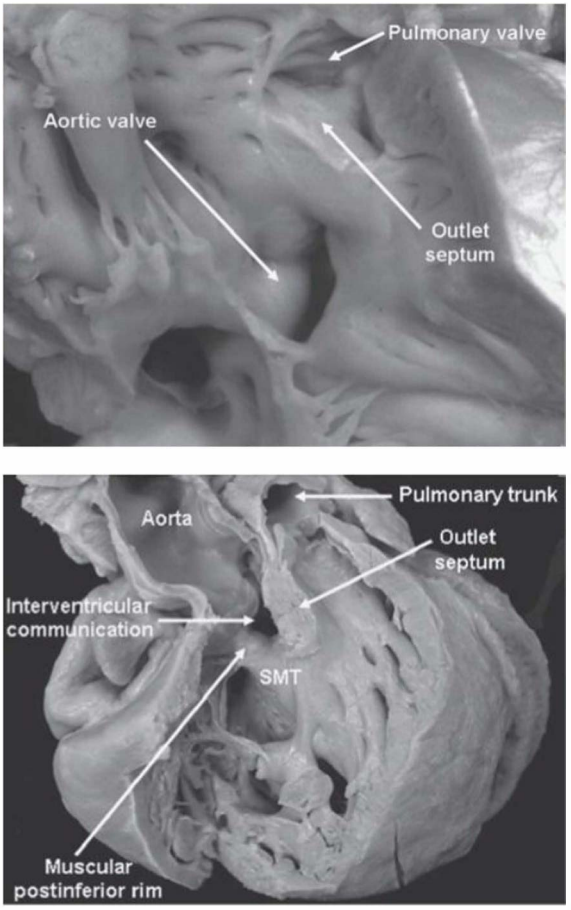



**FIGURE 59-19** These illustrations show the extensive outlet septum, seen in the setting (**A**) of tetralogy of Fallot and (**B**) double-outlet right ventricle.

mitral valve, which has a solitary zone of apposition between its aortic and mural leaflets (Fig. 59-20). The aortic leaflet is relatively short, guarding only about one-third of the valvar circumference, albeit that it has considerable depth.[13] The mural leaflet, although having a much more extensive annular attachment, has much less depth. In most hearts, this leaflet is divided into a series of "scallops," usually three, but five or even six may be seen on occasion. Although guarding different lengths of the junction, the two leaflets have more or less equal surface area. The left ventricle is characterized by its particularly fine trabeculations. Unlike the right ventricle, however, the trabecular component of the left ventricle has a smooth septal surface, down which cascades the fan-like left bundle branch of the ventricular conduction tissues. The outlet portion is well formed in the left ventricle but does not have completely muscular walls because of the fibrous continuity between the leaflets of the aortic and mitral valves. As we have already emphasized, because of the coronet-like attachment of the valvar leaflets (Fig. 59-10), it is inappropriate to describe either

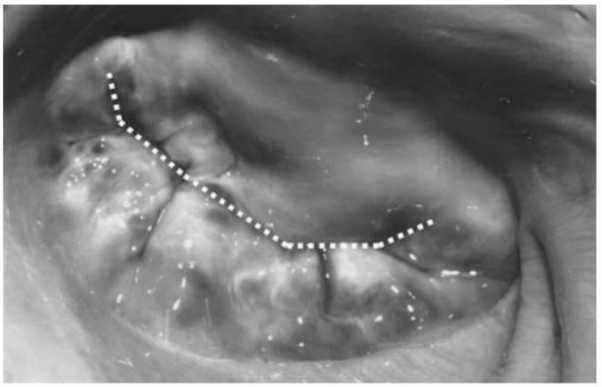


**FIGURE 59-20** The mitral valve is photographed from above with the leaflets in their closed position. Note the solitary zone of apposition of the leaflets (dotted line), which guard markedly dissimilar proportions of the atrioventricular junction. The anterior leaflet is also known as the aortic leaflet of the valve.

arterial valve as possessing an "annulus." It is the semilunar attachments of the valvar leaflets that constitute the surgical "annulus," and it is these structures that the surgeon typically uses as an anchorage for sutures in replacing the aortic valve. We should emphasize again, therefore, that the leaflets are attached within the arterial root in crown-like rather than circular fashion.

## SEQUENTIAL SEGMENTAL ANALYSIS OF CONGENITAL HEART DISEASE

In the preceding paragraphs, we have discussed the basic morphology of the cardiac chambers and emphasized the features of surgical note. Thus far, this has been considered mostly in the setting of the normal heart, albeit with emphasis being placed on the differences seen in the setting of a common atrioventricular junction (Figs. 59-14 and 59-15) or when the ventricular septum itself is deficient (Fig. 59-19). The majority of patients undergoing surgery will have their intracardiac lesions in the setting of the normal heart. Persistent patency of the arterial duct, for example, or a simple aortic coarctation, does not alter the basic cardiac morphology. Similarly, the presence of a simple atrial septal defect does not distort the basic arrangement to such an extent that the heart is not readily recognized as being normal. In a few cases, nonetheless, the anatomy can be exceedingly bizarre, often with the heart itself abnormally positioned. Even in these complex cases, description is straightforward if the surgeon follows the logical approach we have tried to establish in the previous paragraphs. This is because, as we have already discussed, the atrial appendages, the markers of atrial identity, can be arranged in only one of four patterns (Fig. 59-4). Irrespective of these patterns, the ways in which the atrial chambers can connect to the ventricles are also strictly limited, as are the possibilities for the ventricles

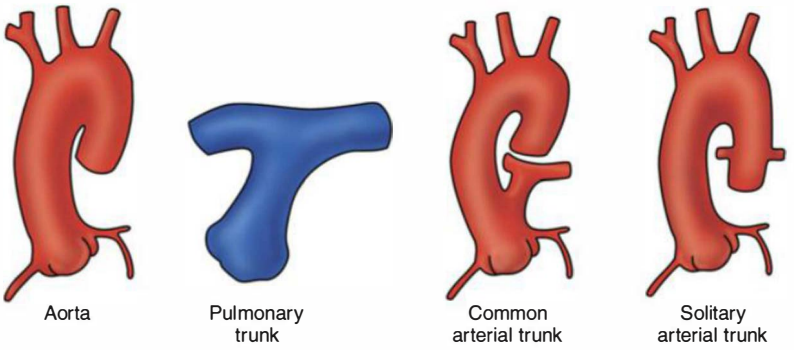



**FIGURE 59-21** The features permitting distinction of an aorta from a pulmonary trunk and a common from a solitary arterial trunk.

to make connection with the arterial trunks. We conclude our discussion of cardiac morphology, therefore, with a brief account of the principles and philosophy of sequential segmental analysis.[1,17]

## Philosophy of Sequential Segmental Analysis

To provide an unambiguous account of any abnormally formed heart, it is necessary to separate, for the purposes of description, the morphology of the individual cardiac segments, the way that the segments are joined one to the other, and the interrelationships of the components within each segment.[17] Provided that each of these features is described using mutually exclusive terms, the specific words themselves are less important, although it surely makes sense to use words in the fashion that they are also employed in day-to-day activities. We have used a multiplicity of terms during the evolution of our own approach. It is these experiences that have convinced us of the value of using simple everyday words in description rather than retaining a lexicon deeply rooted in classic etymology. One of our rules, therefore, is to eschew Latin and Greek words, since American English has now become the scientific "lingua franca." Another of our rules is to follow the "morphologic method." This requires that cardiac components, however deformed or abnormal, should always be identifiable in terms of their own intrinsic characteristics.[18,19] Venous connections, therefore, cannot, for example, be used to identify an atrium, since the veins themselves may connect anomalously. In similar fashion, the structure of an atrioventricular valve cannot always be used as the final arbiter of the morphology of a ventricle, simply because some ventricles do not possess atrioventricular valves. Thus, as we have already discussed, it is the morphology of the atrial appendages that provides the most reliable feature for atrial recognition, and it is the nature of the apical trabeculations that is most useful for distinguishing between the ventricles. Although the arterial trunks have no intrinsic distinguishing features, almost always their pattern of branching is sufficiently discrete to permit distinction of an aorta from a pulmonary trunk and both of these from a common or solitary trunk (Fig. 59-21). On the basis of the philosophy outlined above, it also follows that we always account separately for the way that the cardiac chambers are joined as opposed to their relationships in space. It could be argued that each of these features should then have equal weight in description. There is little doubt, however, that the surgeon is most concerned with the way that the cardiac components are joined or not joined. In our system, therefore, we delegate primary importance to the connections between the cardiac components, relegating relationships to a secondary role.

## Atrial Arrangement

Recognition of the arrangement of the appendages is the starting point of diagnosis. We depicted the four possible arrangements for the appendages in Fig. 59-4. When both morphologically right and left appendages are present, as in the usual and mirror-imaged patterns, the arrangements can be said to be lateralized. The other two patterns are isomeric. As we discussed, it is the morphology of the atrial appendages that dictates the disposition of the sinus node, hence the importance to the surgeon of recognizing the position of the morphologically right appendage.

## Variations at Atrioventricular Junctions

Once the atrial arrangement is known, the other information needed to analyze the structure of the atrioventricular junctions is the morphology of the ventricular chambers. Separate attention should then be paid to the fashion in which the atria are joined to the ventricles and the morphology of the atrioventricular valve or valves, which guard the junctions. The commonest patterns are found when each atrium is joined to its own separate ventricle. Such biventricular atrioventricular connections can be found with either lateralized or isomeric atrial appendages. With lateralized appendages, there are two possible patterns of connection across the atrioventricular junctions (Fig. 59-22). The first gives the concordant pattern and is seen when the right atrium is joined to the right ventricle and the left atrium to

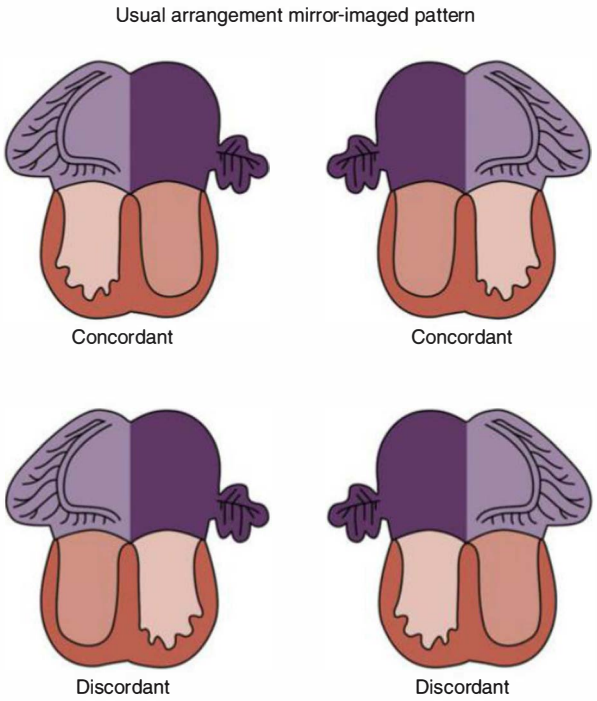



**FIGURE 59-22** The diagram shows the essence of concordant and discordant atrioventricular connections, which can both exist in either usually arranged or mirror-imaged variants.

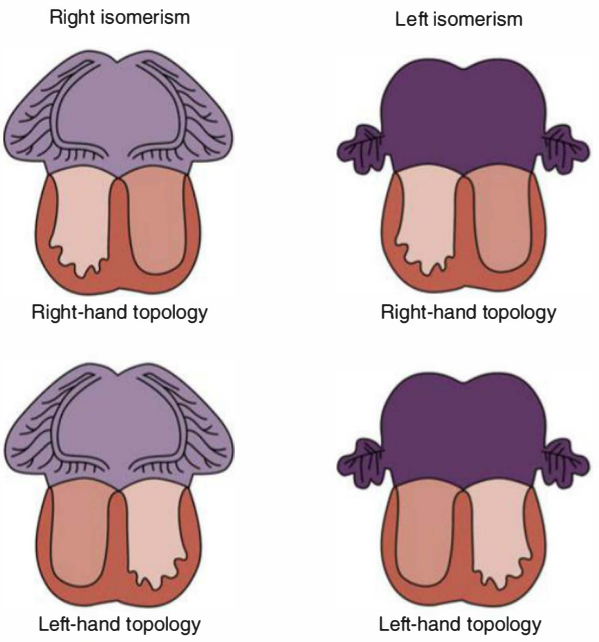



**FIGURE 59-23** When the atrial appendages are isomeric, the atrioventricular connections are perforce ambiguous. Description of ventricular topology is then essential so as fully to characterize the anatomic arrangement.

the left ventricle. In the second pattern, producing discordant connections, the right atrium is connected to the left ventricle and the left atrium to the right ventricle. Should the appendages be isomeric, then irrespective of the arrangement of the ventricles, the atrioventricular connections are biventricular but ambiguous (Fig. 59-23). It is also important in this situation, therefore, to take note of the topologic arrangement of the ventricular mass. There are two basic patterns (Fig. 59-24). In the usual pattern, as seen in the normal heart with usual atrial arrangement and concordant atrioventricular connections, the right ventricle is related to the left ventricle, so that, figuratively speaking, it is the palmar surface of the right hand of the observer that can be placed on the septal surface of the ventricle, with the thumb in the inlet, the wrist in the apex, and the fingers in the outlet. It is appropriate, therefore, to describe this as right-hand topology (Fig. 59-24, left panel). In the mirror-imaged variant, as seen typically in the patient with congenitally corrected transposition, it is the left hand that can be placed on the septal surface of the morphologically right ventricle, hence its designation as left-hand topology (Fig. 59-24, right panel). Either of these two arrangements can be found when hearts with isomeric atrial appendages have biventricular atrioventricular connections (Fig. 59-23). It follows, therefore, that complete description requires an account of atrial arrangement and ventricular topology. The topologic arrangement is also important to the surgeon, since this feature dictates the disposition of the conduction tissues.[4]

There is then a much smaller second group of hearts that do not exhibit biventricular atrioventricular connections, having as their unifying feature the fact that the atria are joined to only one ventricle. Thus, the hearts have univentricular atrioventricular connections.[20] In this group, all variants can exist irrespective of whether the atrial appendages are lateralized or isomeric. The junctional morphologies making up the group are double-inlet ventricle and absence of either the right or the left atrioventricular connection (Fig. 59-25). With any of these patterns,[21] the atria can be connected to a dominant left ventricle, a dominant right ventricle, or a solitary and indeterminate ventricle. When the atria are connected to either a dominant left or a right ventricle, the complementary ventricle is incomplete and hypoplastic, since of necessity it will lack at least the greater part of its inlet portion. Incomplete right ventricles, as found with the atria, are connected to a dominant left ventricle and are always positioned anterosuperiorly relative to the ventricular mass, although they may be either right- or left-sided (Fig. 59-26, right). Incomplete left ventricles, as seen in the presence of univentricular connection to a dominant right ventricle, are always positioned posteroinferiorly, but again may be either right- or left-sided (Fig. 59-26, left). The feature of solitary and indeterminate ventricles is that they do not possess second ventricles.

The arrangement of the atrioventricular valves depends on the number of atrioventricular junctions. In the setting of concordant, discordant, ambiguous, and double-inlet connections, the atria are joined across two atrioventricular

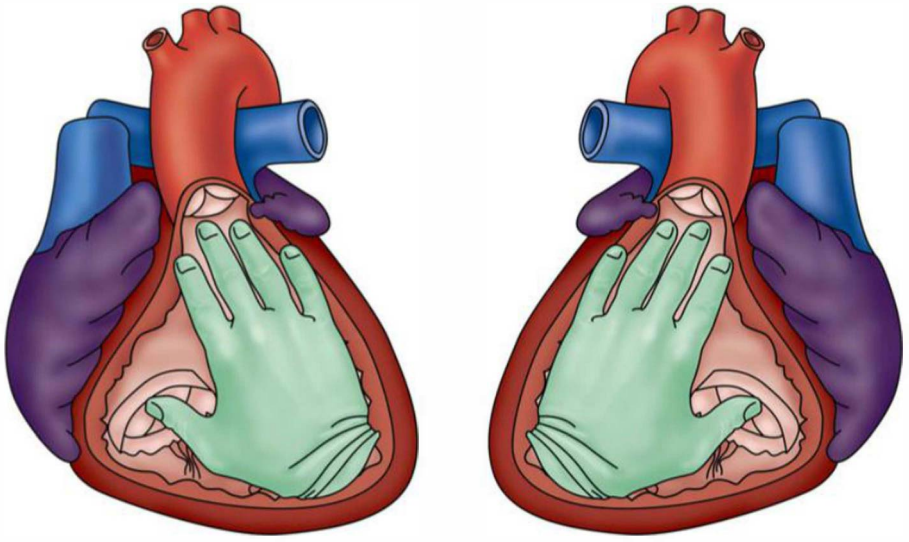



**FIGURE 59-24** The two patterns of ventricular topology, which can be likened to the palms of the hands placed on the septal surfaces of the right ventricles.

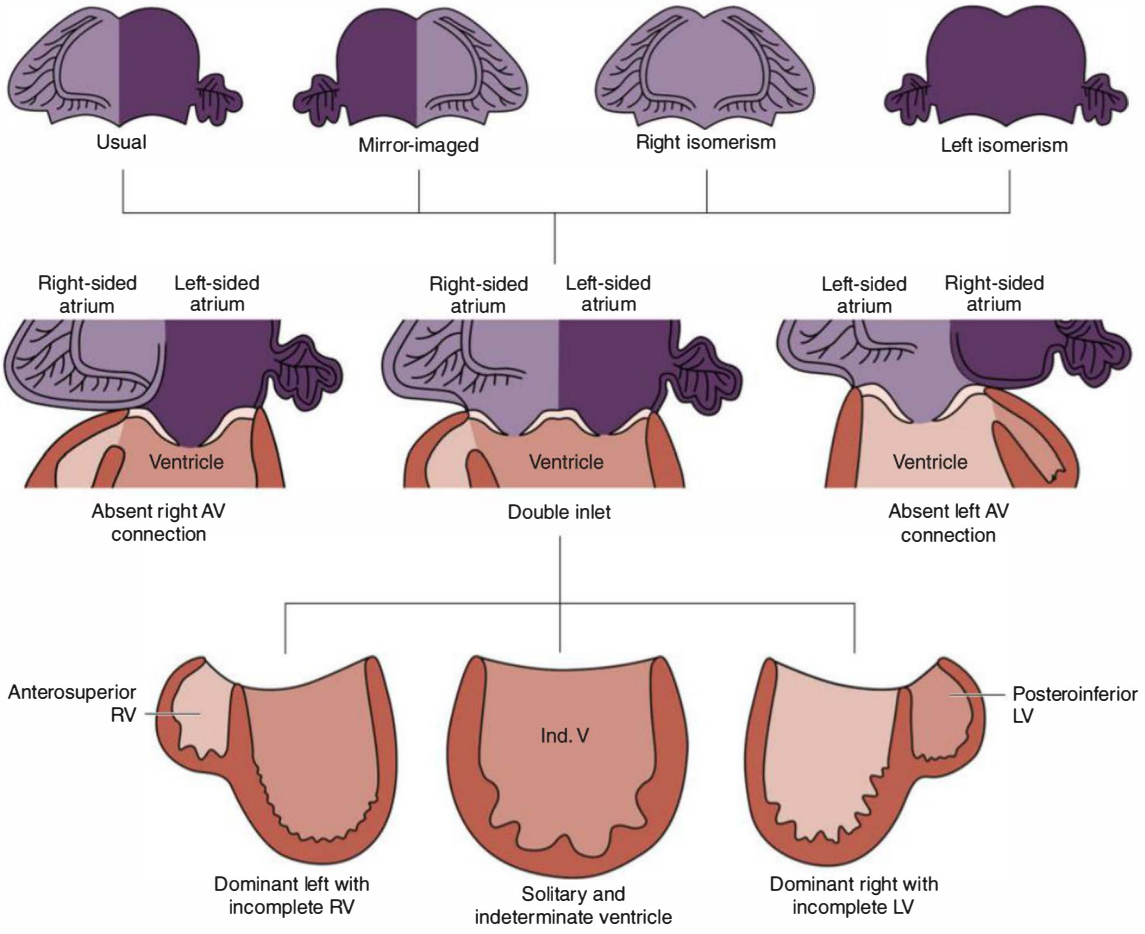



**FIGURE 59-25** The arrangements that produce univentricular atrioventricular connections.

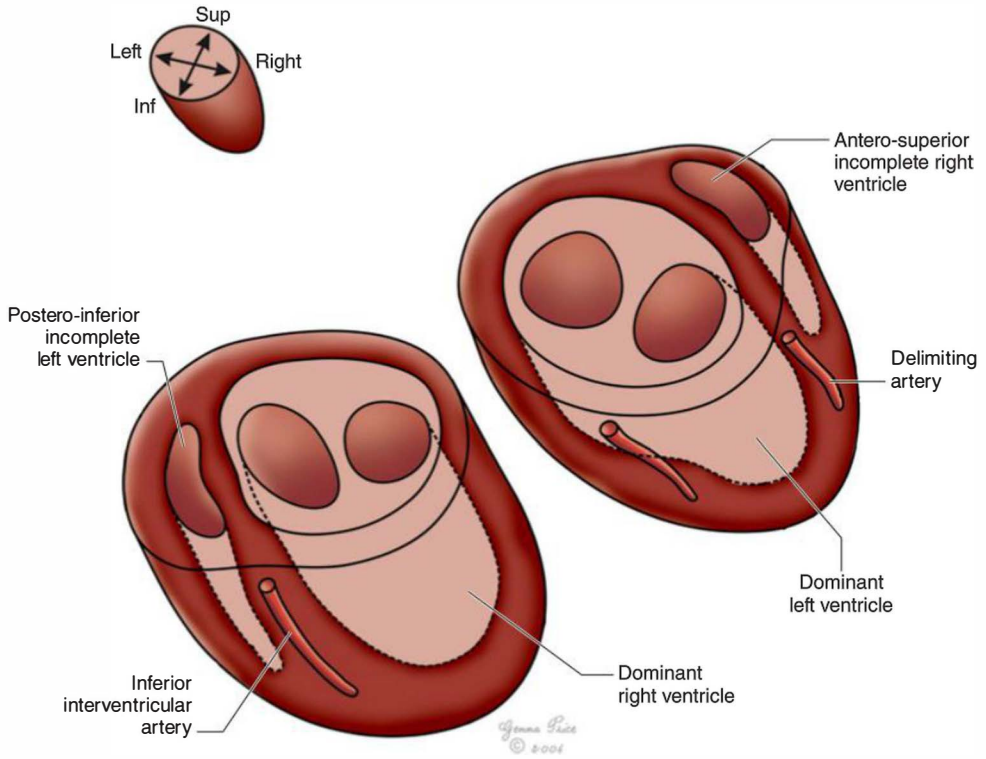



**FIGURE 59-26** The drawing shows how incomplete right ventricles are always found anterosuperiorly relative to a dominant left ventricle, albeit in right- or left-sided position (upper panels), whereas incomplete left ventricles a re positioned inferoposteriorly relative to dominant right ventricles, but again can be left- or right-sided (lower panels).

junctions to the ventricular mass. The dual atrioventricular junctions, however, can be guarded by two separate valves (Fig. 59-11) or by a common atrioventricular valve (Fig. 59-14). One of two valves, or rarely both, may straddle the ventricular septum when the tension apparatus is attached on both sides of the septum. When a valve straddles, usually its junction also overrides the septum. The degree of this override determines the commitment of the valve to the two ventricles. For the purposes of categorization of the precise connection present in such hearts, the overriding valve is assigned to the ventricle connected to its greater part. Common valves usually straddle, but not always. A common valve, nonetheless, always guards two atrioventricular junctions (Fig. 59-13), so note must be taken of this feature in assessing the degree of override. When there are two valves, it is also possible for one of the valves to be imperforate. This morphology must be distinguished from absence of an atrioventricular connection, since both patterns produce atrioventricular valve atresia.[22] When one atrioventricular connection is absent, the modes of connection of the persisting junction are strictly limited. The atrioventricular valve may either be exclusively connected to one ventricle or alternatively straddle or override.[23] The latter arrangement gives a connection that is uniatrial but biventricular (Fig. 59-27).

## Variations at the Ventriculoarterial Junctions

In analyzing the ventriculoarterial junctions, it is again necessary to distinguish between the specific junctional morphology and the structure of the arterial valve or valves guarding the junctions. At this level, attention should also be paid to

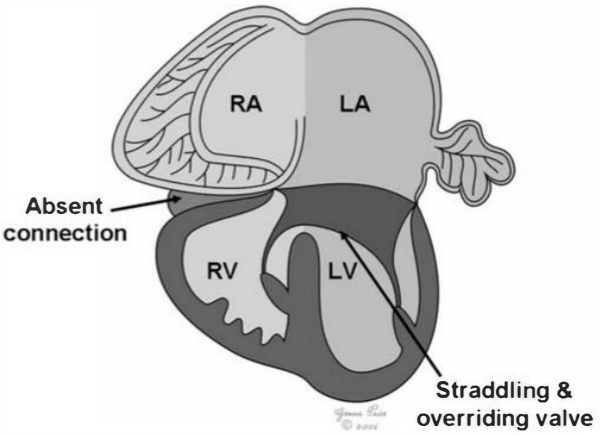



**FIGURE 59-27** The drawing illustrates the uniatrial but biventricular atrioventricular connection.

arterial relationships as well as the morphology of the ventricular outflow tracts (so-called infundibular or conal anatomy).

The ventriculoarterial connections are concordant when the aorta takes origin from the left ventricle and the pulmonary trunk from the right ventricle. When the aorta arises from the right ventricle and the pulmonary trunk from the left ventricle, the ventriculoarterial connections are discordant. These descriptions hold good irrespective of whether the ventricles themselves are complete or incomplete. Double outlet exists when the larger parts of both ventriculoarterial junctions take origin from the same ventricle, which can be of right, left, or solitary and indeterminate morphology. Single outlet from the heart describes the situation in which only one patent arterial trunk can be traced from the ventricular mass. The trunk may be common or solitary (Fig. 59-21) or, alternatively, it may be an aortic trunk with pulmonary atresia or a pulmonary trunk with aortic atresia. Because arterial valves lack tension apparatus, they cannot straddle. Thus, variations in valvar morphology are more limited than for the atrioventricular valves. Furthermore, a common arterial valve exists only when there is a common arterial trunk. When there are two arterial valves, however, one of them may be imperforate. One or both may also override the septum. As with overriding atrioventricular valves, the precise connection of an overriding arterial valve is determined by using the "50 percent" rule.

Arterial interrelationships are of no significance in determining the fashion in which the trunks take their origin from the ventricular mass. Indeed, it is impossible to infer the ventricular connection of the intrapericardial arterial trunks from their relationships. Relationships can be of help in predicting connections. For example, a right-sided and anterior aorta is seen most frequently with concordant atrioventricular and discordant ventriculoarterial connections. At best, however, such associations are no more than a guide to the possibility of abnormal connections. In describing the abnormal relationships, it is also necessary to account for both the positions of the arterial valves and for the orientation of the ascending portions of the arterial trunks. Relationships can be described by accounting for the position of the aortic valve relative to the pulmonary valve, taking note of right/left and anterior/posterior coordinates. For the arterial trunks, the possibilities are for the pulmonary trunk to spiral around the aorta toward its bifurcation, or else for the trunks to ascend in parallel fashion. Combining these two variables makes it an easy matter to describe all anticipated patterns of arterial interrelationships.

In the past, great emphasis was placed on the role of the bilateral conus, or bilateral infundibulum, in diagnosis. Again, however, there is no specificity in these findings. Each arterial valve can potentially be supported by a complete muscular infundibulum irrespective of the ventriculoarterial connection. It is more important, therefore, to analyze the infundibular components. There are three parts of significance.[15] The first separates the arterial valves and their subvalvar outflow tracts from each other. This structure is the muscular outlet—the infundibular or conal septum. The second part is the free parietal component of the ventricular wall. The third part is the inner heart curvature of the ventricles between the atrium and the great arterial trunks. This muscular fold separates the arterial valves from the atrioventricular valves and is well described as the ventriculoinfundibular fold. The most frequent variability in infundibular morphology depends on the integrity of this fold. When it is intact, then there is discontinuity between the atrioventricular and arterial valvar leaflets; in other words there is usually a complete muscular infundibulum or indeed bilateral infundibula (Fig. 59-19B). When the fold is deficient, there is continuity between the leaflets of the atrioventricular and arterial valves, and part of the infundibulum is deficient (Fig. 59-19B). We purposely use the term "usually," since it is rarely possible for the ventriculoinfundibular fold to be intact, producing arterial–atrioventricular discontinuity, and yet for the outlet septum to be deficient, permitting valvar continuity between the leaflets of the aortic and pulmonary valves. In this setting, the muscular infundibula would be incomplete. The integrity of the ventricular outflow tracts, therefore, depends on the morphology of both the ventriculoinfundibular fold and the outlet septum. The interrelationship between these structures is well demonstrated in the "supracristal ventricular septal defect." In the past, such defects were held to be "supracristal" because they were positioned superiorly relative to the so-called septal band (Fig. 59-28A). But the allegedly infracristal defects (Fig. 59-28A) are also positioned superiorly relative to this "band." It is because of such difficulties than we believe it is better to describe the septal band as the septomarginal trabeculation, this being an integral component of the muscular ventricular septum. Nowadays, fortunately, ventricular septal defects are more usually described as being perimembranous, muscular, or doubly committed and subarterial.[24] It is failure of muscularization of the outlet septum, combined with failure of formation of the subpulmonary infundibulum, which is the phenotypic feature of the doubly committed, or supracristal, defect (Fig. 59-28B). There is a common ventriculoarterial junction, albeit guarded by separate aortic and pulmonary valves. The lesion is closely related, therefore, to a common arterial trunk (Fig. 59-29), albeit that the doubly committed defect can be found when both arterial trunks arise from the right ventricle or even when they take their origin predominantly from the left ventricle. Because of this variation, it has been suggested that the lesion would best be described as "double outlet both ventricles."[25]

## Subsequent Steps in Sequential Analysis

The analysis described thus far accounts only for the segmental combination of the heart. In most instances, this will be normal. But it will have cost the surgeon nothing to prove this normality. Indeed, it is essential to do so. Having established the segmental pattern, analysis is concluded by assessing all the associated defects present. This is also best done in segmental fashion, commencing by confirming the normality of the venoatrial connections. Attention can then be

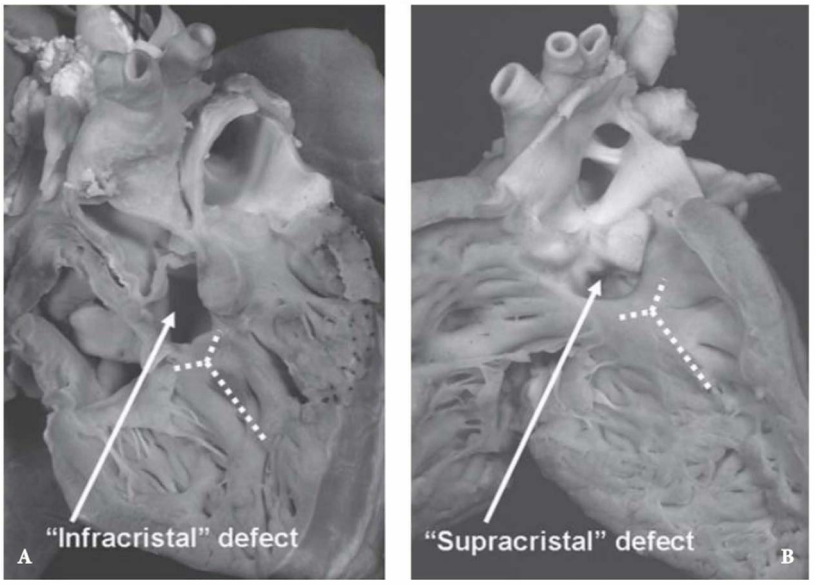



**FIGURE 59-28** The "supracristal" defect (**B**) is compared with the allegedly "infracristal" variant (**A**); in reality both defects are located within the limbs of the "septal band" or septomarginal trabeculation (dotted Y). The phenotypic feature of the supracristal defect, which is doubly committed and juxta-arterial, is failure of muscularization of the outlet septum and failure to form the subpulmonary infundibulum. Because of this, there is a common ventriculoarterial junction.

directed to the atrial segment, the ventricular segment, and the arterial segment in turn, at the same time looking for any junctional malformations that may not have been accounted for during the analysis of the connections. Then the anatomy of the aortic and pulmonary pathways is assessed. In this way, any congenital cardiac lesion or combination of lesions, however simple or complex, is accounted for and understood in the segmental setting of the heart itself. Separate description is then provided for the location of the heart, the direction of its apex, and the arrangement of the thoracic and abdominal organs, taking care to describe each system separately when discrepancies from the anticipated patterns are encountered. To the best of our knowledge, it has proved possible to describe and categorize in unambiguous fashion all lesions thus far known and encountered.

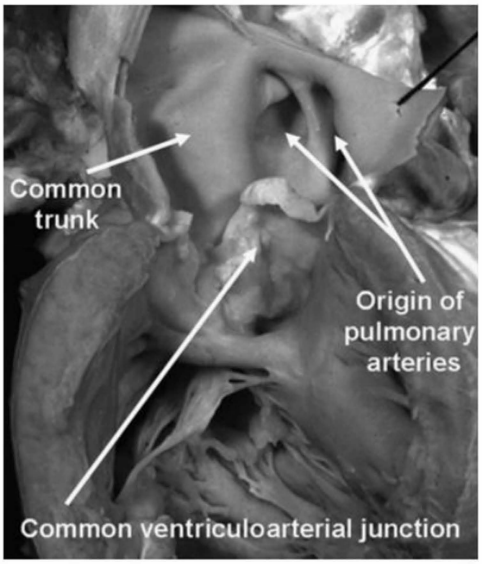



**FIGURE 59-29** The picture shows the doubly committed ventricular septal defect seen in the setting of a common arterial trunk. Note the similarity to the defect shown in Figure 59-28B. The phenotypic feature of both hearts is the common ventriculoarterial junction, albeit guarded by separate aortic and tricuspid valves in the heart shown in Figure 59-28B.

## ACKNOWLEDGMENT

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# Perioperative Critical Care of the Pediatric Cardiac Surgical Patient

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## INTRODUCTION

Perioperative care of the pediatric cardiac surgical patient requires a multidisciplinary team that includes cardiologists, cardiothoracic surgeons, anesthesiologists, and intensivists as well as multiple other support staff. A well-functioning system requires coordinated effort and communication. This chapter focuses on common perioperative critical care challenges encountered in the care of pediatric cardiac surgical patients, with emphasis on physiologic basis, diagnosis, and treatment.

## PEDIATRIC CARDIOPULMONARY PHYSIOLOGY

Management of children with congenital heart disease (CHD) requires an understanding of neonatal/pediatric cardiopulmonary physiology and how this differs from the adult. First, neonatal and pediatric cardiac output (CO) is significantly more reliant on heart rate (vs stroke volume) than in the adult patient. As such, these patients will maintain a "normal" blood pressure despite impending shock by increasing heart rate to maintain CO. The neonatal and pediatric myocardium is less compliant (compared to an older child or adult) and is less tolerant of changes in preload and afterload. Oxygen consumption is also increased compared with adult patients, and lung volumes are obviously smaller. In order to maintain oxygen supply in the face of increased consumption with smaller lung volumes, minute ventilation is increased with higher respiratory rates. In addition, infants breathe below their functional residual capacity (FRC), and lung units are collapsed and reopened with each breath. This unique physiology results in low tolerance to apnea and very rapid desaturation.

Neonates also have potential for labile pulmonary vascular resistance (PVR) as they transition from fetal to newborn circulation in the first few days of life. Furthermore, neonatal pulmonary physiology differs from that of an older child because of the increased chest wall compliance, reliance on the diaphragm for optimal mechanics, and increased propensity for atelectasis. The preoperative management of neonates with significant unrepaired CHD requires an understanding of both general neonatal cardiopulmonary physiology as well as the specific impact of the particular lesion(s).

## PREOPERATIVE CARE

Although the majority of preoperative care of the pediatric patient with CHD is in the outpatient setting, the neonate with significant unrepaired CHD may require intensive care assessment and monitoring. Goals of preoperative care include optimization of hemodynamics to ensure adequate CO and normal end-organ function while awaiting corrective or palliative neonatal surgery.

In general, infants requiring neonatal surgery can usually be classified into three preoperative "states": single ventricle (SV) physiology, transposition physiology, and ductal-dependent pulmonary or systemic blood flow.

1. Many complex congenital heart lesions have **SV physiology,** where there is complete mixing of systemic and pulmonary venous return and thus aortic (AO) saturation equals pulmonary artery (PA) saturation. The total ventricular output is divided between two competing parallel circuits whose flow (pulmonary/systemic) is determined by the resistances of each system. Hypoplastic left heart syndrome (HLHS) typifies SV physiology. Acceptable balance between pulmonary and systemic outputs will provide enough pulmonary blood flow for adequate oxygen delivery without excessive volume load on the SV as

well as adequate systemic output and end-organ function. However, since the two circuits are in parallel, too much blood flow to one system occurs at the expense of the other. The neonate with HLHS requires an unrestrictive atrial-level communication to unload the left atrium and ductal patency [via prostaglandin ($PGE_1$) infusion] to maintain systemic outflow. Too much pulmonary blood flow, manifested as "high saturations," will occur at the expense of systemic output; these infants are at risk for renal insufficiency (due to decreased renal perfusion) and necrotizing enterocolitis (due to decreased splanchnic perfusion).

2. Transposition of the great arteries (TGA), where the aorta arises from the right ventricle (RV) and the PA arises from the left ventricle (LV) (PA saturation is greater than the AO saturation) mandates mixing. This intercirculatory mixing can occur at any of the following levels: intracardiac (via a patent foramen ovale, atrial septal defect or ventricular septal defect) and/or extracardiac (via patent ductus arteriosus). Effective pulmonary blood flow (net volume of blood flow passing from systemic circulation to pulmonary circulation, the anatomic right-to-left shunt) and effective systemic blood flow (net volume of blood flow passing from pulmonary circulation to systemic circulation, the anatomic left-to-right shunt) is the intercirculatory mixing upon which survival depends. Extracardiac intercirculatory mixing is maintained by ductal patency with a $PGE_1$ infusion, while inadequate intracardiac mixing is palliated with a balloon atrial septostomy (BAS) when needed.
3. Finally, **lesions where either pulmonary or systemic blood flow depends on ductal patency** require a $PGE_1$ infusion until palliative or corrective neonatal surgery takes place. Ductal-dependent pulmonary blood flow lesions include tetralogy of Fallot with severe right ventricular outflow obstruction, tetralogy of Fallot with pulmonary atresia, and critical pulmonary stenosis. Critical coarctation of the aorta is another example of a lesion associated with ductal-dependent systemic blood flow.

Indications for preoperative mechanical ventilation in the neonate with unrepaired CHD are commonly due to pulmonary and/or cardiac issues. Causes of respiratory failure are many and may include prematurity with respiratory distress syndrome, meconium aspiration, or infectious etiologies. Cardiac indications are less common, but may include severe hypoxemia due to inadequate intracardiac mixing (neonate with TGA in need of a BAS) or low CO due to increased pulmonary blood flow at the expense of systemic output in the SV patient.

In addition to optimizing pulmonary and cardiac systems, preoperative care of the neonate with CHD should include evaluation of other associated anomalies, including a genetic evaluation as well as head, abdominal, and renal ultrasound where indicated. Blood analysis for genetic abnormalities (including fluorescence in situ hybridization – FISH test) is best performed prior to blood transfusion associated with cardiopulmonary bypass (CPB).

# POSTOPERATIVE CARE

## Admission to the ICU

All children undergoing surgical repair for CHD are admitted to an intensive care unit (ICU) postoperatively. Upon admission, the patient will be quickly assessed by an intensivist for hemodynamic stability including heart rate, heart rhythm, clinical CO, perfusion, adequacy of sedation and/or pain control, and respiratory dynamics. Blood work is sent on admission to assess ventilation and oxygenation, electrolytes, hematocrit, platelet count, and coagulation. A chest x-ray is taken to ensure adequate lung inflation, normal heart size and to confirm proper placement of all lines, tubes, and wires.

Verbal report is given by cardiac surgeons and anesthesiologists to the ICU team upon transfer of care. Report should include the patient's preoperative cardiac anatomy; other significant medical problems; preoperative medications; intraoperative findings and procedure done, including duration of CPB, cross-clamp and deep hypothermic circulatory arrest (DHCA); location of arterial and venous lines; medications required intraoperatively; complications; occurrence of arrhythmias; transesophageal echocardiographic findings; plan, including vital sign goals and anticoagulation plans when applicable (see Table 60-1, sign out components). Patient handover systems and checklists have been studied during transfer of care of cardiac patients and are encouraged to enhance quality of communication and patient safety.[1]

**TABLE 60-1: Components of Postoperative Report**

**Patient name**
**Age**
**Weight**
**Allergies**
**Surgical procedure**

| Preoperative data | Intraoperative Data | Postoperative Data and Plans |
|---|---|---|
| Preoperative diagnosis and anatomy<br>Previous surgeries | Induction and intubation<br>Lines/catheters/chest tubes | Post-CPB rhythm/pacing need<br>Postoperative TEE findings—LV and RV function, residual lesions, others |
| Past medical history<br>Comorbidities<br>Preoperative medications and symptoms | Intraoperative medications<br>Surgical findings/details/complications<br>CPB/XC/CA/MUFF<br>Lowest temperature | Vital sign goals (HR, BP, CVP, $Spo_2$)<br>Anticoagulation plans<br>Anticipated problems<br>Extubation plans |

BP, blood pressure; CA, circulatory arrest; CPB, cardiopulmonary bypass; CVP, central venous pressure; HR, heart rate; LV, left ventricle; MUFF, modified ultrafiltration; RV, right ventricle; $Spo_2$, oxygen saturation; TEE, transesophogeal echocardiogram; XC, cross-clamp.

## Hemodynamic Monitoring and Cardiac Support

Intensive care of neonatal and pediatric patients relies on both indirect assessments of CO and oxygen delivery as well as direct hemodynamic monitoring. Continuous monitoring of heart rate, respiratory rate, blood pressure, and pulse oximetry is standard. Depending on patient age and anatomy, peripheral (radial, ulnar) or central (umbilical artery or femoral artery) arterial blood pressure monitoring is performed. Central lines are usually placed in the internal jugular, subclavian, or femoral vein after induction of anesthesia, while direct atrial lines may be placed intraoperatively. In neonates, umbilical venous lines are often placed postnatally. Central lines are used for administration of vasoactive infusions, fluids, parenteral nutrition and for measurement of central venous pressures. If the central line tip is positioned at the superior cavo–atrial junction, it can be used to sample mixed venous saturation as well.

### POSTOPERATIVE HYPOTENSION

Hypotension in the postoperative period is common and multifactorial. The more common causes are listed in Table 60-2, along with changes in hemodynamics that are unique to each etiology.

### LOW CARDIAC OUTPUT SYNDROME

Low cardiac output syndrome (LCOS) is one of the most important predictors of poor outcome after surgery for CHD.[2] LCOS is a fall in CO with a commensurate increase in systemic vascular resistance (SVR) and PVR, typically occurring between 6 and 18 h after surgery.[3] Clinical signs of LCOS include tachycardia, oliguria, delayed capillary refill, metabolic acidosis, hypotension, and low mixed venous oxygen saturation. The mainstay of treatment of LCOS is anticipation and early identification. With predictable decrease in CO and increased PVR and SVR, afterload reduction (milrinone) and inotropic support oppose this trend.[4]

**TABLE 60-2: Diagnosis of Postoperative Hypotension**

| Clinical Condition | BP | HR | RA/CVP | LA |
|---|---|---|---|---|
| Tamponade | ↓ | ↑[a] | ↑ | ↑ |
| LCOS (with euvolemia) | ↓ | ↑[a] | ↑ | ↑ |
| Hypovolemia | ↔↓ | ↑[a] | ↓ | ↓ |
| AV dissociation | ↓ | AV dissociation | ↑ | ↑ |

AV, atrioventricular; BP, blood pressure; CVP, central venous pressure; HR, heart rate; LA, left atrial pressure; LCOS, low cardiac output syndrome; RA, right atrial pressure.

[a]Sinus tachycardia.

Adapted from Everett AD, Lim DS: *Illustrated Field Guide to Congenital Heart Disease and Repair*. Scientific Software Solutions, 2004–2013.

### POSTOPERATIVE VASOACTIVE MEDICATIONS

Inotropic support is a mainstay of postoperative care. Table 60-3 lists the most common vasoactive medications used for the postoperative pediatric cardiac surgical patient.

## Arrhythmias

Arrhythmias are a common complication after surgical repair of CHD, with a reported incidence of 15 to 30 percent.[5–7] Postoperative arrhythmia prolongs ICU stay and increases morbidity and mortality. Various studies have looked at risk factors for arrhythmias and found age, underlying anatomy and type of repair, duration of CPB, and cross-clamp time to be possible risk factors.[5–7] The most common postoperative arrhythmias are junctional ectopic tachycardia (JET), complete heart block, ventricular tachycardia (VT), and supraventricular tachycardia.

The first step in managing a patient thought to have an arrhythmia is to obtain a 12-lead electrocardiogram (EKG). This should be reviewed by a pediatric intensivist or cardiologist to determine the precise type of rhythm present. If the rhythm is complex, a pediatric electrophysiologist may be consulted. If the patient is hemodynamically unstable as evidenced by poor perfusion on exam, low blood pressure, change in mental status, and metabolic acidosis, prompt diagnosis should be made so that correct treatment may be immediately initiated.

### JUNCTIONAL ECTOPIC TACHYCARDIA

JET is one of the most prevalent postoperative arrhythmias. It is an automatic tachycardia that should be suspected when a patient has a gradual increase to heart rates out of range for age, usually greater than 170 beats/min, over minutes to hours. It typically occurs in the first 24 postoperative hours, but may have a later onset. The exact cause is unknown but it is thought to be due to direct or indirect atrioventricular (AV) node injury, including shear forces and edema. Surgery near the AV node is not required as evidenced by the fact that JET may occur after repair of total anomalous pulmonary venous return, Blalock-Taussig shunts, and Glenn and Fontan procedures.

The EKG shows a narrow complex tachycardia with AV dissociation as evidenced by a ventricular rate faster than atrial rate. P waves may or may not be visualized on the EKG depending upon the speed of ventricular rate. If a central venous line is present, cannon A waves are noted on waveform analysis, representing atrial contraction against a closed tricuspid valve. Differential diagnosis of this narrow complex tachycardia includes sinus tachycardia and supraventricular tachycardia. If the diagnosis is unclear and temporary pacing wires are present, an atrial EKG often aids in the diagnosis. The key pathophysiologic finding in JET is loss of AV synchrony. Postoperative patients have decreased CO secondary to cardioplegia, inflammatory response to CPB, and ischemia-reperfusion injury. Loss of atrial synchrony

**TABLE 60-3: Commonly Used Vasoactive Medications**

| Drug | Mechanism | Inotropy | Chronotropy | SVR | PVR | Dose | Side Effects |
|---|---|---|---|---|---|---|---|
| Amiodarone | Class III antiarrhythmic, but with class IB, II and IV effects | ↔↓ | ↔ | ↔ | ↔ | Load: 1–15 mg/kg<br>Infusion: 5–10 μg/kg/min | Slows repolarization and AV conduction, prolongs QTc |
| Epinephrine | $\alpha_1$- and $\beta_{1,2}$-agonist | + | + | | ↑ | Bolus: 1–10 μg/kg<br>Infusion: 0.05–2 μg/kg/min | Hypertension, tachycardia, arrhythmias, myocardial necrosis |
| Dopamine | Dopaminergic$_1$-, $\alpha_1$- and $\beta_1$-agonist | ↔ | ↔ | ↑ | ↑ | Infusion: 0.5–20 μg/kg/min | Arrhythmias |
| Dobutamine | $\beta_1$-agonist | + | ↔ | ↔ | ↔ | Infusion: 0.5–10 μg/kg/min | Arrhythmias |
| Isoproterenol | $\beta_{1,2}$-agonist | + | + | ↑ | ↓ | Infusion: 0.05–1 μg/kg/min | Arrhythmias |
| Milrinone | Phosphodiesterase-3 inhibitor | + | ↔ | ↓ | ↓ | Load:50 μg/kg<br>Infusion: 0.25–1 μg/kg/min | Hypotension |
| Norepinephrine | $\alpha_1$- >>> $\beta_1$-agonist | + | + | ↑ | ↑ | Infusion: 0.05–0.1 μg/kg/min | Arrhythmias, hypertension |
| Sildenafil | Phosphodiesterase-5 inhibitor | ↔ | ↔ | ↔ | ↓ | PO/NG, starting dose 0.25/mg/kg Q6 h and titrate | Hypotension |
| Vasopression | V 1a agonist | ↔ | ↔ | ↑ | ↔ | Infusion: 0.5–2 mU/kg/min | Bradycardia, hyponatremia |

AV, atrioventricular; QTc, corrected QT interval.

Adapted from Everett AD, Lim DS: *Illustrated Field Guide to Congenital Heart Disease and Repair*. Scientific Software Solutions, 2004–2013.

will further decrease CO and may lead to hypotension. Treatment focuses on decreasing catecholamine infusion, as JET is catecholamine-sensitive. Sympathomimetic drugs, such as epinephrine and dopamine, should be quickly discontinued as they may sustain arrhythmia and cause further hypotension. Patients should be sedated and hyperthermia should be aggressively treated. Active cooling may be necessary in refractory and symptomatic cases. Medical therapy includes amiodarone or procainamide to decrease conduction and control ventricular rate. Both drugs should be administered carefully as hypotension may occur. Atrial pacing may also be used to restore AV synchrony. JET is usually self-limited, resolving within the first postoperative week.

## HEART BLOCK

Heart block is another common postoperative arrhythmia, with complete AV block being the most significant. It results from damage at or below the level of the AV node. EKG shows complete dissociation of the atrial rate from the ventricular rate. The QRS complex may be narrow or wide depending upon where in the ventricular conduction system the injury occurs; injury at the AV node itself will lead to a narrow complex QRS whereas injury to the bundle of His will lead to a wide-complex QRS. Symptoms depend on ventricular rate since this controls CO in these patients. If ventricular rate is sufficient, patients may be asymptomatic. If ventricular rate is low for age, the patient may have signs and symptoms of low CO. For symptomatic patients, AV pacing is the mainstay of treatment. Pharmacologic therapy with sympathomimetics or anticholinergics may increase the atrial rate but will not restore AV synchrony and is therefore not indicated. Most cases of postoperative complete AV block are temporary, and resolve within the first 1 to 2 postoperative weeks. For those that do not resolve, placement of a permanent pacemaker may be necessary.

## VENTRICULAR TACHYCARDIA

VT is another form of arrhythmia seen postoperatively. It is a wide-complex tachycardia and may be nonsustained (resolving spontaneously) or sustained. It may be stable VT with no effects on the patient's hemodynamic status or unstable with complete cardiovascular collapse. Stable VT is treated with lidocaine and/or amiodarone. Correction of electrolyte abnormalities and acid–base status is strongly encouraged. Unstable VT is treated according to Pediatric Advanced Life Support (PALS) guidelines, including rapid defibrillation and chest compressions followed by epinephrine, amiodarone, and/or lidocaine.

## PACING

Many patients have temporary pacing wires placed during cardiac surgery. In particular, patients at risk for postoperative arrhythmias or heart block benefit from pacing. Pacing

wires can be diagnostic (for atrial EKG to determine origin of tachycardias) or therapeutic (pacing during heart block or overdrive pacing for tachycardias). Consultation with a cardiologist or intensivist may be warranted for analysis and management of arrhythmias or complex cardiac pacing.

## Pulmonary Management and Mechanical Ventilation

Ventilation and respiratory mechanics exert strong influences on the hemodynamics of children with CHD, especially after palliative or reparative operations. The effect of positive-pressure ventilation on cardiac performance represents the concept of cardiopulmonary interaction. Increased intrathoracic pressure increases right atrial (RA) pressure, which in turn decreases venous return to the RA, RV preload, and RV output. Effects on the left side of the heart are different. Increased intrathoracic pressure decreases LV transmural pressure, which decreases LV afterload and increases LV output. The impact of positive pressure is accentuated in the heart with compromised or failing function, such as in postoperative LCOS. In the palliated univentricular heart, the effects are somewhat different. For example, increased intrathoracic pressure increases the common atrial pressure, which increases the transpulmonary gradient, which will lead to decreased passive pulmonary blood flow in the postoperative cavopulmonary anastomosis/Glenn or hemi-Fontan patients.

PVR is defined as resistance to blood flow within the lungs, which is influenced by the anatomy of the vascular bed, vascular tone, pulmonary blood flow, and left atrial pressure. Understanding how the manipulation of PVR can influence CO is crucial to the perioperative management of children with complex CHD. Conditions that increase PVR include hypoxia, hypercarbia/acidosis, polycythemia, atelectasis, hyperinflation, CPB, and agitation. Conditions that decrease PVR include oxygen, alkalosis, normal FRC, low hematocrit, and pulmonary vasodilators (inhaled nitric oxide, sildenafil, etc.). Patients at risk for postoperative pulmonary hypertension include patients with increased PVR preoperatively, infants in the first several days of life, patients with pulmonary venous hypertension (e.g., total anomalous pulmonary venous return), older children with uncorrected CHD leading to increased PVR, patients with systemic PA pressure, and infants with Down syndrome. Treatment and prevention of pulmonary hypertension include adequate analgesia and sedation, oxygen, appropriate amount of PEEP to maintain FRC, serum alkalinization, inhaled nitric oxide, milrinone, and avoidance of unnecessary endotracheal tube suctioning. Lung volumes above or below FRC lead to increased PVR, which increases RV afterload and can lead to decreased RV function. In the palliated univentricular heart, the effects are somewhat more complex. For example, lung volumes above or below FRC increase PVR, which decreases shunt flow in postoperative stage I Norwood patients and passive PBF in postoperative cavopulmonary anastomosis/Glenn or hemi-Fontan patients.

## Neurologic Monitoring and Sequelae

As surgical techniques have improved over the past decades, mortality associated with CHD has decreased significantly. Comorbidities and long-term outcomes of these patients have now become areas of great interest. Neurologic protection and cognitive development are two such areas, as follow-up of these patients has revealed a high prevalence of neurologic injury. Studies have shown that approximately 50 percent of school-age children who have undergone cardiac surgery as infants have abnormalities on formal testing.[8] Long-term follow-up studies have revealed deficits with speech and language, inattention and hyperactivity, motor skills, memory, problem-solving, learning disorders, and impaired executive functioning, all affecting quality of life.

In 2002, Mahle et al. published a study in which infants with CHD underwent preoperative and postoperative magnetic resonance imaging (MRI).[9] Twenty-five percent of the infants had preoperative abnormalities; early postoperative MRI showed, however, new periventricular leucomalacia in 48 percent, new infarct in 19 percent, and new parenchymal hemorrhage in 33 percent. In summary, new lesions or worsening of preoperative lesions occurred in 67 percent of patients. The causes of neurologic injury in this population are thought to be multifactorial. Preoperative factors include genetics, disturbed cerebral blood flow secondary to cardiac disease and abnormal brain development in utero. Intraoperative factors include exposure to anesthesia, CPB and, in some cases, DHCA, altered cerebral autoregulation/perfusion, and embolism. Postoperative factors include low CO, sedation, possible infection, and emboli. CPB is an extremely important factor when considering intraoperative brain injury. Conditions encountered on bypass include induced hypothermia, transfusion of blood products, hemodilution, altered blood flow characteristics, hypoxia-ischemia, inflammatory response, and reperfusion injury.

Given that neurologic injury is now widely acknowledged in this population, neuroprotection in the perioperative period has become an important focus of study.[10] Detection of injury remains difficult, however. Patients are sedated and often hemodynamically unstable, making clinical and radiographic assessment difficult. Although a head ultrasound can be performed at the bedside, it remains only as a viable option in infants with an open fontanelle. Computed tomography provides more detail than head ultrasound, but MRI is nevertheless the gold standard, with clear elucidation of gray and white matter injury in both cerebral cortex and brain stem. MRI, however, requires transport to a scanner and anesthesia in an often unstable patient. It also does not allow real-time detection of changes during perioperative management.

Near-infrared spectroscopy (NIRS) is one method being used to monitor perioperative brain perfusion. NIRS uses wavelengths of light to measure oxyhemoglobin saturation of tissue approximately two centimeters beneath the probe. It is a local marker of brain oxygenation and is used intra- and postoperatively at many institutions to give information on

cerebral perfusion. It is thought to be an early warning sign of neurologic injury. Electroencephalograms (EEG) have been widely studied for the detection of brain injury as evidenced by seizures; however, the results are varied. In addition, there is concern that brain injury is detected once cellular damage has already occurred. Therefore, EEG is not routinely used for the acute detection of brain injury. Biomarkers are another area of intense study as they may be rapid surrogates of injury that can easily be obtained from serum and indicate the presence and extent of injury as well as the response to potential therapies. Biomarkers such as neuron-specific enolase and S100β have been studied and found not to be specific for brain injury. Newer biomarkers such as glial fibrillary acidic protein (G-FAP), ubiquitin C-terminal hydrolase 1, and phosphorylated axonal neurofilament heavy chain show promise as brain-specific biomarkers.

## Hemostasis and Coagulopathy

Cardiac surgery and CPB both require and cause coagulopathy. The impact of CPB on hemostasis is greater in the pediatric patient than in adults and postoperative bleeding is a significant problem. Risk factors for postoperative bleeding and transfusion include younger age, higher preoperative hematocrit, complexity of surgery, duration of DHCA, low core body temperature, and platelet count during CPB.[11] Causes include activation and consumption of clotting factors, hemodilution, platelet dysfunction, inflammatory mediators, and effects of medications.

CPB has been shown to activate the clotting cascade via intrinsic (contact) and extrinsic pathways, causing thrombin formation and decreases in fibrinogen and platelet number and function. Hypofibrinogenemia and thrombocytopenia have been associated with increased intraoperative and postoperative blood loss in children undergoing cardiac surgery.[12] Platelets are impacted in multiple ways during pediatric cardiac surgery. Platelets are significantly decreased by the trauma of CPB and hemodilution. Platelet function is decreased in children by CPB, hypothermia, heparin, and protamine. In addition, CPB-stimulated proinflammatory mediators such as interleukin-1, tumor necrosis factor, and endotoxin activate and impair the coagulation cascade.[13]

Younger age, and smaller weight and body surface area have been shown in multiple studies to be risk factors for postoperative bleeding and transfusion.[11,14] This is presumably due to the greater magnitude of hemodilution and CPB effect on smaller children as well as intrinsic coagulation abnormalities in neonates and small infants.

Diagnosis and management of postoperative coagulopathy in neonates and children begin with a thorough evaluation of laboratory data immediately on admission to the ICU. Hemoglobin, platelet count, prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen concentration should be obtained. Thromboelastography (TEG) can provide an evaluation of the comprehensive system of clot formation and breakdown. In anticipation of laboratory data, immediate drainage from chest tubes should be replaced empirically, typically with packed red blood cells and fresh frozen plasma (FFP) or fresh whole blood. In the patient with severe or persistent bleeding, early platelet administration may be prudent considering their importance in clot formation and the high likelihood of thrombocytopenia in the infant and child with significant bleeding after CPB. Similarly, fibrinogen may need repletion with either FFP or cryoprecipitate.

Multiple small case series report off-label use of Factor VIIa for severe bleeding in postoperative cardiac patients. Although most report decreased chest tube output and decrease in PT/PTT without increase in thrombotic complications, caution must be used in administration of this agent to patients with shunts or conduits. Data to support safety of this agent in patients following congenital heart surgery are insufficient.

If severe or persistent bleeding is present after correction of coagulopathy and repletion of platelets and fibrinogen, reexploration may be warranted.

## Fluid Imbalance/Electrolyte and Renal Management

Despite routine use of modified ultrafiltration after CPB, fluid overload and renal dysfunction are major contributors to morbidity after neonatal and infant surgery.[15] Total body water accumulation is directly proportional to duration of CPB.[3] Use of diuretics is routine in the postoperative period.

Need for renal replacement modalities in the postoperative pediatric patient is not uncommon. Indications include fluid overload, electrolyte abnormalities, and uremia. Renal replacement modalities include peritoneal dialysis, hemodialysis, and continuous arteriovenous or venovenous hemofiltration with or without dialysis. Selection of a renal replacement therapy depends on volume and/or solute to be cleared, patient's age and vascular access, weight, and comorbidities.

The postoperative myocardium is extremely sensitive to electrolyte imbalances. Postoperative care should be attentive to the maintenance of normal serum electrolytes. Hypocalcemia, hypomagnesemia, and hypokalemia should be quickly remedied, as these imbalances may lead to arrhythmias. Use of steroids on CPB can cause postoperative hyperglycemia with a concomitant high output diuresis leading to hypovolemia. Fluid replacement is the treatment. Hyperglycemia is common early after neonatal and pediatric cardiac surgery, particularly after glucocorticoid administration, but will generally resolve without treatment. The significance of hyperglycemia and need for treatment in this patient population is controversial. In a large retrospective review of infants and children undergoing cardiac surgery, hyperglycemia was associated with increased risk of complications such as infection, need for extracorporeal membrane oxygenation (ECMO), lactic acidosis, organ system failure, and death, but this risk was modified by younger age and residual cardiac lesions.[16,17] However, other studies have found that postoperative hyperglycemia is not associated with increased

morbidity or mortality, or does not have a deleterious effect on neurodevelopmental outcomes at 1 year of age.[18–20]

## Infectious Issues

Pediatric cardiac surgical patients are at high risk for infections in the postoperative period. Many surgical patients are neonates with immature immune systems. In addition, postoperative patients may experience immunosuppression secondary to critical illness. These patients also have wounds, central lines, and prosthetic materials used in their repair, which may become colonized with bacteria. One recent study found the prevalence of nosocomial infections in pediatric cardiac surgery patients to be approximately 25 percent.[21] Postoperative infections prolong ICU length of stay and increase morbidity and mortality.

Patients routinely receive perioperative antibiotic coverage to prophylax against skin flora; however, this is discontinued within 24 hours, and longer treatment is not supported. It is common for patients to have fever in the immediately postoperative phase as part of a systemic inflammatory response to bypass; this should resolve within 24 hours. Infection should be considered in any patient who experiences profound hypotension. In addition, if fever continues for greater than 24 hours or resolves and then recurs, an infectious workup should be performed including complete blood count, blood culture, urinalysis and urine culture, and gram stain and culture of respiratory secretions in intubated patients, as well as a complete physical exam. Differential diagnosis of fever in a postoperative patient includes superficial wound infection, mediastinitis, osteomyelitis of the sternum, bacteremia, urinary tract infection, and ventilator-associated pneumonia, or tracheitis in ventilated patients. In addition, during the winter season, viral infections such as respiratory syncytial virus and influenza should be considered. These may be community-acquired in patients presenting for surgery from home or nosocomial. Secretions should be sent for rapid assay and viral culture as part of the infectious workup to rule out viral infection.

Given the prominent use of central lines in this population and the prevalence, morbidity, and mortality associated with catheter-related bloodstream infections in ICU patients, prevention of this nosocomial infection has become an area of interest for those caring for these patients. One recent study looked at risk factors for bloodstream infection in pediatric cardiac ICU patients and found that, in surgical patients, lower admission weight, higher Pediatric Risk of Mortality (PRISM) and Risk Adjustment in Congenital Heart Surgery (RACHS) scores, greater blood product exposure, prolonged mechanical ventilation, and noncardiac comorbidities were risk factors for catheter-related bloodstream infections.[22]

Treatment of postoperative infection depends upon etiology. If bacterial infection is suspected, empiric broad-spectrum antibiotics should be started while the workup is being done. If a bacterial source is found on culture, specific treatment is based on the type of bacteria and the location of infection.

The most important aspect of infections in postoperative patients is prevention. Devices such as central lines and urinary catheters should be placed in a sterile manner. Access to central lines for intermittent medication administration and blood draws should be minimized and all devices should be removed as soon as possible.

Special mention should be given to patients with the DiGeorge syndrome. This is caused by a deletion of the long arm of chromosome 22 and is associated with cono-truncal abnormalities, such as truncus arteriosus and interrupted aortic arch, as well as tetralogy of Fallot. An additional component of the syndrome is T-cell immunodeficiency due to hypoplasia or agenesis of the thymus. Humoral deficiency may also be present. This further predisposes this group of patients to perioperative infections as well as risk of graft versus host disease associated with blood transfusion. If DiGeorge syndrome is confirmed, an immunologist should be consulted for further testing and management.

## Postoperative Cardiopulmonary Arrest

Cardiac arrest (CA) is more common in the patient with cardiac disease than in patients without heart disease but outcomes are better. In a large review of pediatric perioperative CA, the incidence of CA for patients undergoing cardiac procedures was 127 per 10,000 versus 2.9 per 10,000 for noncardiac procedures.[23] Children with CHD are more likely to arrest from cardiovascular causes than children without heart disease, whose CA etiology is primarily respiratory. In the postoperative period, LOCS, arrhythmias, bleeding, and mechanical problems such as shunt occlusion are risks for CA in cardiac patients. In a dedicated pediatric cardiac ICU, survival for cardiac patients receiving cardiopulmonary resuscitation (CPR) following cardiac surgery was reported to be 46 percent, increasing to 53 percent for patients receiving CPR following cardiac surgery.[24]

Treatment of CA requires prompt recognition and CPR of excellent quality. The 2005 American Heart Association (AHA) CPR guidelines stress minimizing chest compression interruption and avoidance of hyperventilation to improve flow to critical organs during CPR. After sternotomy, reopening of the chest provides for evaluation and treatment of tamponade as well as direct cardiac compressions.

Consideration of the patient anatomy, physiology, and surgical procedure must factor in to resuscitation plan during CA following cardiac surgery. In patients with shunt-dependent pulmonary blood flow, shunt occlusion should be entertained, particularly in patients with low end-tidal carbon dioxide despite quality CPR. In addition to standard AHA guidelines, heparin should be considered for treatment of urgent shunt occlusion.

An additional adjunct is mechanical support in the form of rapid deployment ECMO for rescue from CPR (eCPR). eCPR can provide restoration of oxygenation and perfusion to vital organs while the cause of CA is investigated and treated. When CA is recognized promptly and quality CPR initiated, eCPR can lead to very good outcomes, even

**TABLE 60-4: Approaches to Clinical Scenarios in Stages of Single Ventricle Heart Disease Palliation**

| | Stage I—Norwood Procedure | Stage II—Cavopulmonary Anastomosis Glenn or Hemi-Fontan Procedure | Fontan Completion |
|---|---|---|---|
| **Postoperative considerations** | Systemic arterial saturation of 75% correlates with a $Q_p$:$Q_s$ = 1 | Minimization of SVC–PA to atrial pressure gradient by:<br>• Early extubation<br>• Elevation of head<br>• Reduction of pulmonary edema(diuretics)<br>• Monitor for pleural effusions | Arrhythmias:<br>• Postoperative period: sinus node dysfunction<br>• Late: atrial arrhythmias<br>Ventricular dysfunction |
| **Low CO** | • Poor contractility = inotropes<br>• Arrhythmia = restoration of sinus rhythm<br>• Maldistribution of blood flow due to pulmonary overcirculation[a] or valvar regurgitation = afterload reduction | | • Hypovolemia = volume<br>• Increased PVR<br>• Obstruction in systemic venous pathway |
| **Hypoxemia-etiologies** | • Low PV saturation = lung disease, pleural effusion, or pneumothorax<br>• Low systemic venous saturation = anemia, low CO, or increased $O_2$ consumption<br>• Decreased $Q_p$:$Q_s$ = shunt/conduit obstruction, severely elevated PVR, restrictive atrial septum (can treat acutely by raising the systemic BP) | • Elevated PVR<br>• Arteriovenous communications<br>• Venous collaterals<br>• SVC–PA obstruction | • Low PV saturation > lung disease, pleural effusion or pneumothorax<br>• Fenestration too large or a leak in lateral tunnel<br>• Decompressing veins<br>• Pulmonary AVMs |

AVM, arteriovenous malformation; BP, blood pressure; CO, cardiac output; $O_2$, oxygen; PA, pulmonary artery; PV, pulmonary vein; PVR, pulmonary vascular resistance; $Q_p$:$Q_s$, ratio of pulmonary to systemic blood flow; SVC, superior vena cava.

[a]Pulmonary overcirculation due to arch obstruction needs to be addressed by surgical or catheter intervention.

Adapted from Everett AD, Lim DS: *Illustrated Field Guide to Congenital Heart Disease and Repair*. Scientific Software Solutions, 2004–2013.

in patients who have had CPR for over 30 min and would have otherwise died. A retrospective review of a large single-center experience with eCPR in cardiac patients reported survival to discharge of 51 percent, despite CPR durations of over 30 min in some cases; 75 percent of those had mild-to-no neurologic impairment (see Chapter 87).[25]

## Special Considerations for the Postoperative Single Ventricle Patient

SV physiology encompasses a wide variety of anatomic lesions that have parallel circulations and complete mixing of systemic and pulmonary venous return. Palliation for SV anatomy in most centers is performed via two to three stages, with variability in the initial procedure depending on degree of left ventricular outflow tract obstruction and amount of pulmonary blood flow. The goal of the stage 1 palliation with modified Blalock–Taussig shunt or Sano modification is 3-fold: creation of unobstructed systemic blood flow by construction of a neo-aorta, unobstructed pulmonary venous return by an atrial septectomy, and controlled pulmonary blood flow without PA distortion. The goals of second stage or cavopulmonary anastomosis Glenn/hemi-Fontan procedure are two: volume unloading the SV and creation of passive pulmonary blood flow. The final stage or Fontan completion provides in-series pulmonary and systemic circulations (see Chapter 77). Table 60-4 shows the three stages with their unique postoperative considerations, as well as our approach to low CO and hypoxemia.

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## PERIOPERATIVE CRITICAL CARE OF THE PEDIATRIC CARDIAC SURGICAL PATIENT BOARD REVIEW QUESTIONS (CHAPTER 60)

1. Which is correct regarding postoperative arrhythmias?
   A. The incidence is 5 to 10 percent
   B. JET typically occurs after the first 24 h
   C. Most cases of postoperative complete AV block are temporary
   D. VT is a narrow complex tachycardia
   E. Prolonged AO cross-clamp time is not a risk factor
2. Which of the following decreases PVR?
   A. Hypoxia
   B. Acidosis
   C. Polycythemia
   D. Agitation
   E. Sildenafil
3. Which is not a risk factor for postoperative pulmonary hypertension?
   A. Neonatal repair
   B. Total anomalous pulmonary venous return
   C. Older child with uncorrected congenital defect
   D. Patients with normal preoperative PA pressures
   E. Down syndrome
4. Which of the following is not a risk factor for neurologic injury?
   A. Anesthesia
   B. Hypothermic circulatory arrest
   C. Blood transfusion
   D. Hemoconcentration
   E. Reperfusion
5. Which is not a risk factor for bloodstream infection in the pediatric ICU?
   A. Lower admission weight
   B. Lower PRISM score
   C. Blood product exposure
   D. Prolonged mechanical ventilation
   E. Renal dysfunction

## ANSWERS

1. **Answer: C.** Most cases of postoperative complete AV block are temporary. The overall incidence of arrhythmia is 15 to 30 percent. JET typically occurs during the first 24 h after surgery. VT is a wide complex tachycardia. Prolonged AO cross-clamp and CPB times are associated with increased incidence of postoperative arrhythmias.
2. **Answer: E.** Sildenafil is a pulmonary vasodilator. The other conditions increase PVR.
3. **Answer: D.** Patients with normal PA pressures prior to operation are not at increased risk for postoperative pulmonary hypertension. The remaining conditions are associated with increased risk.
4. **Answer: D.** Hemodilution from CPB, not hemoconcentration, is associated with neurologic injury. The remaining conditions are all associated with the development of neurologic injury during repair of CHD.
5. **Answer: B.** A higher PRISM or RACHS score is associated with an increased risk of bloodstream infection. Lower admission weight, greater blood product exposure, prolonged mechanical ventilation, and other comorbidities are all established risk factors as well.

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# Cardiopulmonary Bypass in the Pediatric Patient

*Jacob Ostrowsky*
*Ross Ungerleider*

The development of cardiopulmonary bypass (CPB) has enabled operative treatment for countless numbers of patients with a multitude of acquired and congenital cardiac and vascular anomalies. The CPB circuit is a unique device designed to divert a patient's circulation around the area that requires surgical repair so that surgeons can operate in a virtually bloodless field. The typical CPB circuit consists of a series of blood pumps that provide cardiopulmonary support through disposable components consisting primarily of tubing, a blood collection reservoir, and an oxygenator (Fig. 61-1). The deoxygenated venous blood is pumped through the oxygenator and is returned to the arterial system of the patient. The first successful open heart surgical procedure using an extracorporeal CPB machine was performed in 1953 by John Gibbon.[1] Since then, there have been dramatic improvements to the device itself, to the components required for its application and to the techniques and strategies used to apply it, and to the monitoring, while safety systems have been designed to enable safe and consistent results, with steadily improving patient outcomes. This chapter will provide a general overview of the CPB circuit components [extracorporeal circuit (ECC)] and a brief discussion of strategies used to apply this technology in the field of pediatric cardiac surgery.

## CIRCUIT COMPONENTS

### Venous Cannulae

Deoxygenated blood is diverted from the systemic atrium to the collection reservoir via a venous cannula. Although CPB can be simply established using a single venous cannula placed in the right atrium, most pediatric operations require direct or indirect (via the right atrium) systemic (or bicaval) venous cannulation. As the situation warrants, venous drainage may be achieved through peripheral cannulation of one or more of the large peripheral veins. This is particularly true for larger children, in which femoral vessels might be sizeable. For smaller children and infants presternotomy cannulation of the internal jugular vein in the case of a truly hostile mediastinum might be an option for venous drainage. The diameter of the venous cannula/e depends on the size of the patient, the number of cannulae, and the desired CPB blood flow rates for the particular child and operation. Venous drainage is normally facilitated by gravity, but may be assisted by adding low-level vacuum, allowing in turn for the use of smaller venous cannulae. The vacuum is applied to the venous reservoir in the circuit, and should not exceed a negative pressure of 40 mm Hg. The potential drawback for vacuum assisted venous drainage is air entrainment and hemolysis through excess negative pressure; when applied appropriately, this risk of such complications is nevertheless minimal.[2,3]

### Tubing

The venous cannulae are connected to tubing that provides a path for blood volume to be diverted to a reservoir. The tubing is made of polyvinyl chloride, causing foreign surface activation of blood components that requires systemic anticoagulation with heparin to avoid clotting of the CPB circuit. Coated tubing, lined with heparin or a biologically active surface, is currently available and is used by many centers in an attempt to mimic the vascular endothelium and minimize the activation of clotting and inflammatory pathways. Tubing is available in many sizes, ranging from ⅛″ to ½″ inner diameter. Selecting the proper size is based on the requirements for calculated CPB blood flow rates.

### Blood Pumps

There are two common types of blood pumps available: roller pumps and centrifugal pumps. Roller pumps consist of two roller heads placed 180 degrees apart inside a raceway. Tubing is placed between the roller heads and the raceway and, as the rollers spin, blood is propelled forward in the same direction as the rotation of the roller head. Roller pumps require partial occlusion of the tubing to ensure blood flow in the proper direction. Pump output is measured by the speed of rotation and the diameter of the tubing. Centrifugal pumps

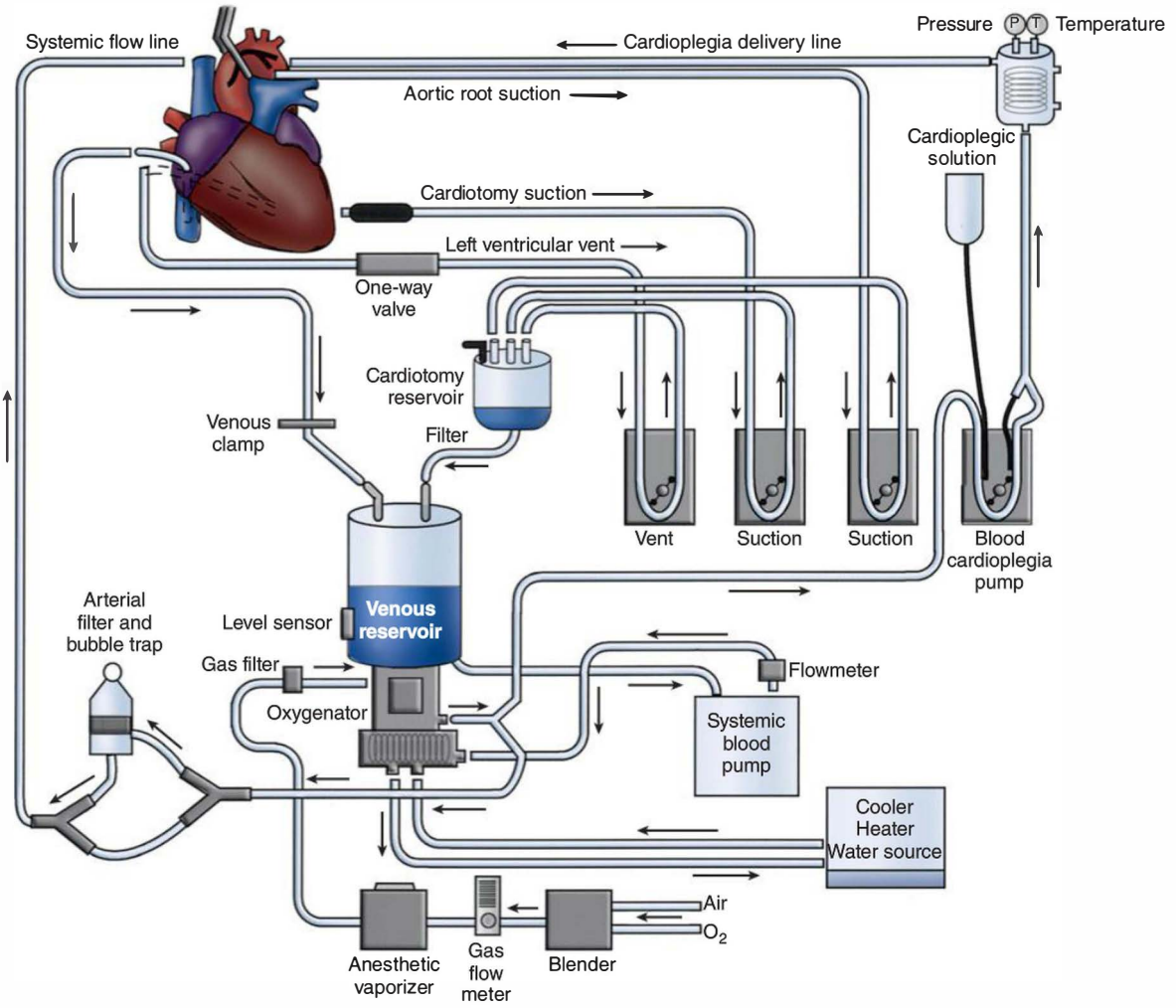



**FIGURE 61-1** The typical CPB circuit consists of a series of blood pumps that provide cardiopulmonary support through disposable components consisting primarily of tubing, a blood collection reservoir, and an oxygenator.

have a rotating impeller in the blood compartment that propels blood forward. Centrifugal pumps are nonocclusive, and are therefore dependent on the amount of volume available on the inflow side and the resistance on the outflow side. Pump output is measured by a flow probe placed distal to the outlet of the pump. Both pump systems can be monitored and regulated with integrated safety devices to avoid air emboli and overpressurization of the ECC.

## Oxygenator

The oxygenator is the component of the circuit that allows for blood to upload oxygen and unload carbon dioxide. In modern circuits, the blood chamber or surface is separated from gas surface by a polypropylene or silicone membrane (see also Chapter 87). The gas flow is regulated by a blender that enables manipulation of oxygen content, and the speed at which the gas passes through the membrane is known as "sweep speed." This creates a pressure gradient for both oxygen and carbon dioxide that facilitates gas exchange via diffusion across the membrane, similar to the alveolar capillary interface within the lung. Inhalational anesthetic can be delivered to the patient by including a vaporizer, inserted inline with the ventilation gas.

## Heat Exchanger

Most oxygenators have an integral heat exchanger that enables manipulation of the patient's core temperature. This is particularly important in neonates and small children, in which hypothermia is still widely utilized. Water lines are attached from a heating and cooling device that allow for precise and efficient temperature control. Maintaining proper temperature gradients during cooling and warming

is important to avoid bubble formation. Overheating blood beyond 40°C carries the risks of severe deleterious effects, such as enzyme and protein inactivation.

## Blood Filters and Arterial Cannula

Most venous reservoirs contain a depth filter to remove gross particles and facilitate air bubble purging. Once the blood has passed through the oxygenator, the inclusion of an arterial line filter is common. The arterial line filter is a screen with a defined pore size to remove particulate and gaseous emboli before the blood is returned to the patient via the arterial cannula. The arterial cannula is typically placed in the ascending aorta, but can be placed in a multitude of sites depending on the pathology and type of repair planned. Other common sites include the axillary or subclavian or right brachiocephalic artery (sometimes through a Goretex© graft), or the femoral artery (also occasionally through a graft). In particular cases (interrupted aortic arch or certain variants of hypoplastic left heart syndrome), the aortic return line may be split, to allow simultaneous proximal and duct-dependent perfusion or selective antegrade cerebral perfusion during aortic arch reconstruction. Proper selection of the arterial cannula size is based on patient size, calculated CPB blood flow rates, and number of cannulae required.

## Cardioplegia Delivery System

To allow surgical repair, it is usually necessary to induce diastolic chemical arrest by using a high potassium solution (cardioplegia). This solution can be crystalloid-based, blood-based, or a combination of the two, for instance, given at 4:1 blood to crystalloid ratio. Although institutional variance is great, most pediatric cardiac centers utilize cold cardioplegia, which maximizes suppression of myocardial metabolism. Typical cardioplegia delivery systems consist of a bubble trap, a heat exchanger, and a pressure monitor. When the heart is isolated from the systemic perfusion by placement of the aortic cross clamp, cardioplegia can be delivered directly within the aortic root with a separate catheter (antegrade). Alternatively, in cases with aortic valve regurgitation, cardioplegia can be infused directly within the coronary ostia. Experience with retrograde (via the coronary sinus) delivery of cardioplegia in pediatric patients is not ubiquitous, but reported. There is also great variability between centers in the timing of redosing of cardioplegia during cardioplegic arrest. This interval ranges from redosing every 30 min (with a lower volume) to the performance of long and complex repairs with a single upfront dose of cardioplegia. This is particularly applicable with crystalloid or very diluted (1:4 blood to crystalloid ratio) solutions.[4,5]

## Vents, Cardiotomy Suction, and Cell Saver

The left ventricle (LV) receives blood throughout CPB from the bronchial circulation via the pulmonary veins and vents placed in the left side of the heart can keep the heart empty and the surgical field more "bloodless." This is particularly true for patients with profound and persistent cyanosis, in whom development of aortopulmonary collaterals is prominent. In order to keep the heart empty, vents are occasionally placed into the left atrium or LV, most commonly through the right superior pulmonary vein (SPV). In very small neonates and infants, insertion of a vent in the right SPV might result in stenosis, or might be unfeasible because of the size of the vessel. Venting can be accomplished through the left atrial appendage, in a retrograde fashion via the pulmonary artery or through a patent foramen ovale, or atrial septal defect (ASD). The surgeon must individualize the venting strategy according to the specific lesion and clinical situation. For example, in the correction of transposition of the great arteries (see Chapter 74) venting through the SPV during cooling or cardioplegic arrest might be unnecessary if an ASD is present or if the neonate has undergone a preoperative balloon atrial septostomy. When the heart is reperfused, venting becomes necessary when the atrial communication has been closed. Occasionally, venting is accomplished through the pulmonary artery or the LV apex.

Vents are connected to the CPB circuit using one of the cardiotomy suction tubes. The cardiotomy suction tubes are small lengths of tubing that are designed to return blood, via a roller pump, back to the CPB circuit. Once the patient is heparinized, blood loss in the surgical field can be removed and returned to the venous reservoir. This diminishes blood loss by returning "shed blood" to the circuit where it can recirculate. Some centers will also return shed blood using a "cell-saver" device, which does not return the blood to the venous reservoir, but functions instead as a suction device. Blood is collected in a chamber from which it can be processed to eliminate the serous component. Blood from the cell-saver often has a hematocrit in excess of 70 percent or greater and is reinfused to minimize the need for blood transfusion. The cell saver can be used regardless of whether the patient is anticoagulated or not, and is often used prior to heparinization and then after administration of protamine. Minimizing the length of tubing and miniaturization of the CPB circuit, as well as priming the circuit with patient's own blood prior to instituting CPB have enabled many centers to avoid blood transfusion altogether, even in small patients.

# CARDIOPULMONARY BYPASS MANAGEMENT TECHNIQUES

## Priming the Circuit

For adults and adolescents, the ECC is primed with a balanced and buffered electrolyte solution. Blood is rarely necessary unless the patient is anemic before surgery. Priming the ECC for neonates and small infants represents a challenge because the volume required may exceed the patient's blood volume, causing excess hemodilution. The average priming volume for most neonatal circuits, including all

components, is 300 to 400 mL. Even at this small volume, blood is often required to maintain adequate oxygen carrying capacity. With the addition of bank blood, other additives are often necessary to normalize the prime.

## Anticoagulation

Exposure of blood to the ECC surface activates the clotting cascade. Without systemic anticoagulation, the patient's blood will clot and obstruct the oxygenator. Unfractionated heparin is the most common drug used to achieve anticoagulation due to simple monitoring with activated clotting time (ACT) and reversal with protamine sulfate. Initial heparin dose of 300 to 400 u/kg is given intravenously or directly into the right atrium prior to cannulation, with a target ACT of greater than 400 s, monitored every 30 to 60 min on CPB. Heparin works by increasing the action of antithrombin III (ATIII). Inadequate anticoagulation with proper heparin dose may be a result of ATIII deficiency. This situation may be corrected by giving exogenous ATIII or fresh frozen plasma.

After separation from CPB, protamine sulfate is infused to bind and inactivate heparin, reversing anticoagulation, and facilitating postoperative hemostasis. Empirical protamine dose of 1 mg for every 100 u of heparin may be used if a direct heparin content assay is unavailable. The protamine/heparin complex can activate complement and stimulate mast cells to release histamine and both can cause cardiac dysfunction and transient hypotension. In neonates and infants, this is usually reversible with simultaneous intravenous administration of calcium. Protamine alone can, however, also stimulate secretion of thromboxane $A_2$ from platelets, causing severe pulmonary vasoconstriction and systemic circulatory collapse. During protamine administration, the surgical team must be prepared to reheparinize and reinstitute CPB in the event of dangerous hemodynamic instability.

## Flow Rate and Pressure

An adult anesthetized and normothermic patient requires a CPB blood flow rate of 2.2 to 2.4 L/min/$m^2$ body surface area for adequate oxygen delivery to the tissues. Neonates and infants require higher flow rates (150–200 mL/min/kg) to meet metabolic demands. Combined with adequate flow rates, maintaining minimal perfusion pressure is crucial to protect vital organ systems. For adults, a mean arterial pressure (MAP) of 50 to 70 mm Hg is considered safe at normal body temperature. MAP below 45 mm Hg for prolonged periods at normothermia is associated with increased neurologic impairment postoperatively. Neonates and infants have compliant vascular beds, making them more flow than pressure-dependent. Perfusion pressure greater than 30 mm Hg is considered adequate in newborns, rising to adult levels only once adolescence is reached. Perfusion pressures can be manipulated by changing CPB blood flow rates or by administering vasoconstricting or vasodilating medications.

## Hematocrit

Appropriate levels of hemoglobin must be maintained to provide adequate oxygen-carrying capacity. Individual tolerance levels dictate the need for transfusion and can be monitored by several methods, including saturation of venous blood ($SVo_2$), cerebral and regional oximetry, CPB blood flow rates, and MAP. As blood viscosity increases with cooling, blood flow through the microcirculation may be impaired, a phenomenon known as "sludging." Matching core temperature to hematocrit (20 percent hematocrit at 20°C as an example) is an accepted practice to avoid sludging. Data in children suggest that sludging does not occur, and that a higher hematocrit of approximately 30 percent carries more benefit during deep hypothermia.[6]

## Temperature

Systemic cooling during cardiac operations while on CPB decreases metabolic activity and suppresses the oxygen demand, allowing reduction of CPB blood flow rates without compromising oxygen delivery to the tissues. Decreased flow may improve visualization of the operative field, enabling a safe and precise surgical repair. Systemic cooling also affords a safety margin in the event of an unanticipated intraoperative catastrophic event. With deep hypothermic conditions, total cessation of blood flow for short periods of time is possible, and the resulting bloodless field may allow the surgeon to deal with a difficult portion of the repair. During aortic cross-clamping, hypothermia also minimizes the rewarming of the myocardium, providing additional myiocardial protection during the ischemic period. Hypothermia in neonates and infants does, however, have postulated disadvantages (capillary leak, prolonged mechanical ventilation, and renal impairment), and some prominent centers have advocated complex cardiac intervention at near-normothermia, with high flow and high hematocrits.

## Neuroprotection

Organ protection is a vital component to proper performance of CPB. Cerebral tissue has high metabolic oxygen demand. At core temperatures below 22°C, cerebral autoregulation (the maintenance of cerebral blood flow across a wide range of perfusion pressures) is impaired.[7–10] Cerebral monitoring is a useful tool to ensure adequate perfusion delivery. Cerebral metabolism is a direct function of brain temperature. Monitoring cooling at multiple sites (including nasopharyngeal, bladder, rectal, and blood) provides information that is useful in determining flow rates on CPB in children. Indirect monitoring of cerebral metabolism during systemic cooling may be achieved via internal

jugular venous saturation with values greater than 95 percent signifying minimal oxygen extraction and adequate cerebral oxygen delivery for the metabolic state of the brain. Electroencephalographic (EEG) monitoring may be used to measure adequate depth of anesthesia, but using EEG as an end point for cooling is unreliable because EEG activity does not always become silent at a consistent body temperature. Near-infrared spectroscopy (NIRS) has become a useful noninvasive tool to monitor cerebral and regional oxygen saturation. The NIRS probe is placed over the tissue of interest, and using optical reflectance a beam of light passes through the area and oxygen saturation is calculated and displayed. Placed over cerebral tissue, NIRS provides an accurate trend of brain oxygen saturation levels which allow real-time interventions to avoid cerebral ischemia.[11]

## Circulatory Arrest and Low-Flow Perfusion in Pediatric Patients

Deep hypothermic circulatory arrest (DHCA) is a useful method to allow surgical repair in a motionless, bloodless field. The patient's temperature is gradually lowered to 18 to 20°C using CPB over several minutes. Perfusion is stopped and the patient's blood volume is drained into the venous reservoir; the cannulae may be removed to improve visualization of the surgical field. Indications for DHCA may include correction of complex congenital systemic or pulmonary venous return anomalies or repairs on the distal pulmonary arteries, aortic arch, or management without clamping of a heavily calcified aorta. The brain has the lowest tolerance to ischemia during DHCA. Inadequate cooling may lead to cerebral rewarming during DHCA, which may result in neurologic injury. Cooling for 20 min or greater is prudent to ensure adequate and homogeneous suppression of cerebral metabolic activity; in addition, packing the head in ice during cooling has the theoretical advantages of rapid and uniform cooling to prevent rewarming during DHCA.[12] Since long duration of the circulatory arrest period is clearly associated with increased frequency of brain injury, it is therefore crucial to limit the arrest period to the absolute shortest time required to achieve the surgical objective. The duration of "safe" DHCA is dependent on numerous factors, including degree and homogeneity of brain cooling, hematocrit, acid–base strategy used during cooling (with pH Stat being best) and the patient's inflammatory state, among other factors. In general, at 18°C, it is not recommended to extend the uninterrupted period of DHCA beyond 40 min.[13,14] Some authors believe the "safe" period at 18°C to actually be no longer than 30 min. Strategies of intermittent, or continuous regional cerebral perfusion have replaced the use of extended, uninterrupted periods of DHCA at many centers.[15–17] The benefits of continuous or intermittent cerebral perfusion compared to limited uninterrupted DHCA (<40 min) have not been proven.[18] Since systemic inflammation (which affects brain response to CPB) is increased at hypothermic temperatures, some centers are limiting systemic cooling to 25°C, by using very limited (<10 min) periods of circulatory arrest, alternating with periods of perfusion, with the patient's head packed in ice, with excellent results. The strategies for neuroprotection have gradually moved to shorter durations of circulatory arrest, more application of continuous cerebral perfusion, decreased levels of systemic cooling (at centers that use continuous or intermittent perfusion), and more routine application of perioperative neurological monitoring with NIRS. Institutional variation and experience dictates the management strategy. The ideal temperature, flow rates, hematocrit and duration of low-flow, and intermittent periods need to be studied further to develop an evidence-based approach to optimize outcomes.

## Weaning from Cardiopulmonary Bypass

Several criteria must be fulfilled before weaning the pediatric patient from CPB. The heart must regain sufficient function to provide adequate cardiac output and the lungs must have satisfactory gas exchange prior to separation from CPB. Factors that have an impact on cardiac and pulmonary function must be assessed and abnormalities corrected before weaning. Temporary pacing may be used to increase a slow heart rate and nonsinus rhythm may benefit from electric cardioversion. Inadequate cardiac contractility should be treated with inotropic agents. If hypothermia was used during CPB, the patient should be fully rewarmed to a core temperature of greater than 35.5°C. Inadequate rewarming, especially in infants, can lead to "rebound" hypothermia with deterioration of myocardial function. Adequate rewarming is vital to hemostasis because the coagulation system functions optimally at normal body temperature.

Blood gas analysis should be performed to normalize blood pH and correct any electrolyte imbalance. Acidosis can negatively influence cardiac contractility. Hyperkalemia is uncommon in patients with normal renal function, but hypokalemia may need correction due to diuresis while on CPB. Ionized calcium may be low due to hemodilution or transfusion of citrate-containing blood products and may be easily corrected while still on CPB. Hyperglycemia can be treated with insulin, mild anemia is usually not a problem with normal LV function, but is not well tolerated with minimal cardiac reserve or in pediatric patients with significant left-to-right shunting and abnormal arterial oxygen saturation.

Anesthetic requirements are decreased during hypothermic CPB due to suppressed metabolism of these agents. Increased levels of anesthetics and muscle relaxants are required during rewarming to prevent patient awareness and shivering. The lungs are inflated before separation from CPB to treat atelectasis. Impaired lung expansion suggests either bronchospasm (which can be treated with bronchodilators) or mucous plug obstruction (which should be cleared with endotracheal suctioning). Care must be taken when passing a suction catheter to avoid mucosal trauma and bleeding in a fully anticoagulated patient. If the pleural space was violated

during surgery, any residual fluid volume should be aspirated to facilitate lung expansion.

Weaning from CPB is performed by partially occluding the venous line to leave volume in the heart. The increase in preload encourages ejection and transition from mechanical to physiologic cardiac output. As more volume is left in the heart, the support is simultaneously decreased from the ECC while assessing hemodynamic parameters. The process is continued until the totality of cardiac output is being entirely provided by the patient's own heart. After assessing adequate hemodynamic stability, the cannulae may be removed and heparin reversed to achieve hemostasis.

Prior to decannulation and reversal of anticoagulation, adequacy of the repair is confirmed in most centers by transesophageal echocardiography, and sometimes requires direct assessment of cavitary pressures or shunt calculation by saturation measurements.

## Postcardiopulmonary Bypass Adjuncts

Once separated from CPB, there is often residual blood volume left in the ECC. There are several methods employed to utilize this volume, including modified ultrafiltration (MUF), cell saver, and whole blood collection systems. MUF is performed using a hemoconcentrator, or artificial kidney, to remove excess volume while reinfusing blood volume left in the ECC. Benefits of MUF include increasing the hematocrit, removing inflammatory mediators, and reducing organ edema. The efficacy of MUF has been shown in pediatric patients, especially neonates and infants, but the time required to remove enough volume to demonstrate clinical significance for larger patients has hampered its utilization in larger patients.[19–24] Autologous blood salvage, commonly known as "cell saver," allows processing of collected shed blood and residual pump blood. Collected red blood cells are separated and washed, removing waste, medications, and damaged cells, and allowing reinfusion to the patient. Cell saver's product consists of red blood cells suspended in saline, and does not contain clotting factors or significant amounts of heparin. Care must be taken when returning large volumes of cell saver due to dilution of clotting factors and the subsequent potential for bleeding. Returning whole pump blood to the patient, either directly or to a collection system, is another way to decrease waste volume in the ECC. Pump blood still contains heparin; therefore, additional protamine may be needed when utilizing this volume.

# COMPLICATIONS OF CARDIOPULMONARY BYPASS

All major organ systems can be adversely affected by a period of CPB. Excess hemodilution combined with hypothermia may cause coagulopathy and platelet dysfunction, leading to postoperative bleeding requiring transfusion of clotting factors and platelets. Foreign surface activation stimulates the systemic inflammatory response syndrome (SIRS) that may result in capillary leak and increased tissue and organ edema. Pulmonary, renal, and hepatic dysfunction may prolong the recovery period, although these issues typically resolve shortly after cessation of CPB support. Brain tissue carries the largest risk for injury following CPB, and this is especially true following excessive periods of DHCA. Neurologic symptoms are usually related to global cerebral ischemia or inadequate perfusion. Seizures, although rare, are usually temporary and do not require long-term medical management. Seizures may be related to embolic events rather than ischemia. Choreoathetosis, thought to be due to basal ganglia ischemia, may occur after periods of DHCA. This very rare event may occur 2 to 6 days after surgery and permanent hypotonia may occur in the most severe cases. By utilizing temperature-corrected blood gas management techniques and limiting duration of hypothermic circulatory arrest with low flow and intermittent reperfusion, many of the clinically significant complications of CPB with DHCA have been reduced.[25]

The evolution of our understanding of the negative sequelae associated with CPB has driven research to reduce the risk of exposure. SIRS was thought to be a product of CPB, but off-pump data have identified it as a mechanism that manifests even without CPB related to incision and surgical exposure. The severity of SIRS can be exacerbated by CPB due to foreign surface activation, and this can be ameliorated by decreasing the surface area and using biologically active surface coatings to decrease blood reactivity. The current-generation CPB machines focus on mast-mounted remote-controlled blood pumps that allow dramatically shorter tubing length to reduce surface area of the ECC. Another benefit of decreasing the size of the ECC is reduced need for blood products, reducing the risks associated with banked blood such as disease transmission, anaphylactic reactions and an overall correlation with blood transfusion and poor outcomes. Avoiding blood prime may also be aided by autologous priming techniques, utilizing the patient's blood volume to prime the ECC will decrease hemodilution and the need for blood transfusion. Autologous priming must be done carefully to avoid hypotension and a subsequent catecholamine response that may compromise global perfusion, particularly in small patients that may not tolerate a large fluid shift. Ultrafiltration techniques allow mechanical fluid manipulation to decrease tissue edema, improve oxygen carrying capacity by increasing hemoglobin concentration, and remove inflammatory mediators.

Cardiopulmonary bypass has been used for more than 50 years to allow cardiac surgical repair for a myriad of people worldwide. Improved surgical techniques, ECC miniaturization, coated tubing, and perfusion management techniques have all contributed to making CPB safer, yielding consistent results. The addition of monitoring systems, such as transesophageal echocardiography and NIRS, has been invaluable in facilitating real-time response in the surgical correction of congenital heart disease.[25]

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# 62 Palliative Operations for Congenital Heart Disease

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*Gordon A. Cohen*

## INTRODUCTION

Alfred Blalock and Helen Taussig ushered in the surgical treatment of congenital heart disease with the introduction in clinical practice of a systemic artery-to-pulmonary artery (PA) shunt in 1944. In the current era of early complete correction of congenital heart disease, the Blalock–Taussig shunt still plays an important role in the surgical management of newborns and infants with inadequate pulmonary blood flow.[1–3] The paradigm shift emphasizing early complete repair is based on contemporary data demonstrating the deleterious effects of palliative physiology, coupled with the realization that most infants can tolerate operative correction. However, some malformations still require a staged approach toward eventual correction, while others may necessitate a palliative procedure when anatomic or patient factors preclude complete repair. A staged repair is often favored when there are extenuating technical issues that stem from morphologic complexity or severe extracardiac pathology that would make one-stage correction prohibitive. The functionally single ventricle (Chapter 77) is an example of this strategy, by which a staged palliative approach eventually achieves the goal of separating the pulmonary and systemic circulations.

Palliative or staged procedures are primarily designed to modify pulmonary blood flow, enhance intracardiac mixing, or rehabilitate a ventricle prior to definitive surgery. For example, aortopulmonary shunts will increase pulmonary blood flow, while a pulmonary artery band (PAB) will limit pulmonary perfusion. Although conceptually simple, palliative operations pose several unique challenges. Intraoperatively, the infants are often low birth-weight or even preterm, and might have other extracardiac factors that have mitigated against complete repair. Postoperatively, the palliated state complicates patient management, as equipoise must be achieved between the pulmonary and systemic circulations (Chapter 60), also inviting the opportunity for interstage attrition.

## SYSTEMIC-TO-PULMONARY SHUNTS

As early complete repair has become increasingly more common, indications for systemic-to-PA shunts are in some respects controversial. However, a shunt still remains the initial procedure for duct-dependent single-ventricle lesions and also specific lesions with inadequate pulmonary blood flow in the presence of two adequate ventricles. In those instances, a systemic-to-PA shunt may be necessary for early survival, at the expense of further surgical procedures.

A systemic-to-PA shunt could be indicated in any anomaly that presents with obstruction of blood flow either entering or exiting the right heart (in specific types of tricuspid atresia, or pulmonary stenosis or atresia not amenable to percutaneous intervention, for example). Other indications include anomalies with unbalanced pulmonary blood flow where a systemic-to-PA shunt (alone or, rarely, with a PAB) can be used to provide a controlled source of pulmonary blood flow.

### Classic Blalock–Taussig Shunt

The development of palliative procedures began at the Johns Hopkins Hospital with the goal of providing improved blood flow to the pulmonary vascular bed in cyanotic children; the subclavian-to-right PA shunt was introduced clinically in 1944.[3] This method of systemic-to-PA shunt followed the pioneering experimental work by Alfred Blalock and Vivien Thomas, who created a canine model of PA hypertension by anastomosing the subclavian artery to the transected end of the PA; this concept was adopted as a palliative attempt to augment pulmonary blood flow in patients with tetralogy of Fallot. In the 2 years following the first successful case, hundreds of cyanotic children traveled to Baltimore to undergo a classic Blalock–Taussig shunt. The reported early mortality was 16 percent, and only 6 percent of the patients were refused surgery.

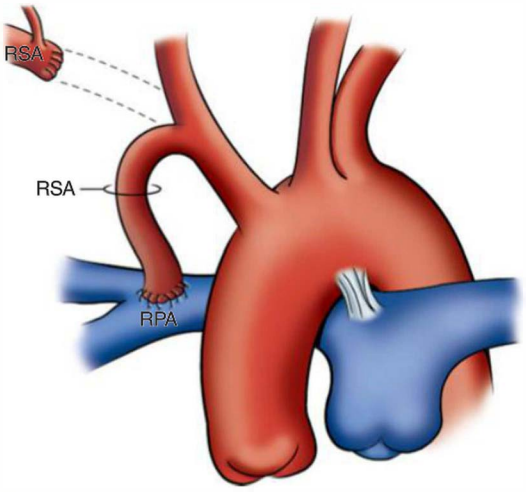



FIGURE 62-1 Classic Blalock–Taussig shunt. RPA, right pulmonary artery; RSA, right subclavian artery.

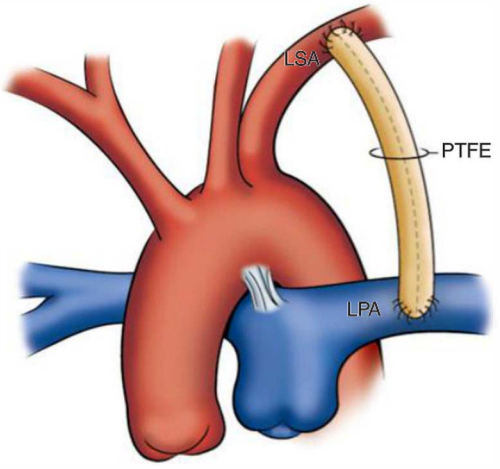



FIGURE 62-2 Modified Blalock–Taussig shunt. LPA, left pulmonary artery; LSA, left subclavian artery; PTFE, polytetrafluoreethylene shunt.

The shunt is performed on the side opposite the aortic arch, by anastomosing the subclavian artery to the ipsilateral PA in an end-to-side fashion. There is usually an innominate artery on the side opposite the aortic arch, and it provides adequate length and orientation to allow for the subclavian to form a gentle curve inferiorly toward the PA. Access to the subclavian artery is typically obtained via an anterolateral thoracotomy (Fig. 62-1). The branches of the subclavian artery are also ligated. Additional mobilization can be obtained by freeing the proximal carotid artery from surrounding tissues. The subclavian artery is then brought through the loop of the recurrent laryngeal nerve, oriented down toward the PA, and sewn to the main PA. Division of the inferior pulmonary ligament will often help in facilitating this anastomosis.

Even though the classic Blalock–Taussig shunt has the distinct advantage of avoiding the use of prosthetic material, this procedure has been largely abandoned because of concerns regarding ipsilateral arm or hand ischemia. Although an asset in the era preceding the advent of open cardiac surgical intervention, the growth potential of this shunt may provide excessive pulmonary blood flow and therefore additional volume-load to the ventricle, which can be extremely detrimental in single ventricle patients. At the time of corrective surgery, the shunt may be taken down via median sternotomy by entering the plane posterior to the superior vena cava (SVC).

## Modified Blalock–Taussig Shunt

A significant modification of the classic Blalock–Taussig shunt, first performed by Redo and Ecker in 1963, involved the interposition of a prosthetic graft to connect the systemic circulation to the PA (Fig. 62-2).[4–6] This procedure was later reported by Gazzaniga in 1976 and termed the "modified" Blalock–Taussig shunt by deLeval in 1975.[7] This modification provides several advantages over the standard Blalock–Taussig shunt: less tendency to deform hypoplastic PAs, less need for mediastinal dissection, preservation of upper extremity blood flow, consistent shunt flow (regulated by the internal diameter of the ostia of the innominate or subclavian arteries), and adequate length. Disadvantages include a 10 to 15 percent incidence of seroma formation and the rare possibility of endocarditis or thrombosis (3–5 percent). Because of these significant advantages, the modified Blalock–Taussig shunt remains the most widely used systemic-to-PA shunt today. Initial concerns that there may be a risk of impaired growth of the contralateral PA have been discredited by current literature, which demonstrates that equivalent growth without distortion can be accomplished with the modified shunt.[5] Compared to the classic Blalock–Taussig shunt, the modified Blalock–Taussig shunt has a more predictable life span, which is limited by the lack of growth potential. These shunts are destined for short-interval use and generally require some other surgical intervention to provide a reliable source of pulmonary blood flow as the child grows.

The modified Blalock–Taussig shunt can be performed through either right or left thoracotomy, or via a median sternotomy. The decision to perform a sternotomy versus a thoracotomy is usually dictated by surgeon preference. However, in some circumstances the approach is dependent on the vascular anatomy and on the location of the ductus arteriosus. For instance, the shunt should be placed on the side of the dominant SVC (so as to facilitate pulmonary arterioplasty at the time of bidirectional cavopulmonary shunt placement) and opposite to the ductus arteriosus. The three different approaches have subtle advantages and disadvantages. Some authors have suggested that a right-sided shunt is easier to take down, while others suggest that a thoracotomy is preferred because, at the time of the next operation, the

pericardium will be relatively free of adhesions. A median sternotomy prevents post-thoracotomy scoliosis, allows for duct ligation, a shorter and more centrally located shunt with less distortion and eventual loss of the upper lobe PA branch, and affords the ability to initiate cardiopulmonary bypass in case of hemodynamic instability or intolerable levels of hypoxemia. Currently, the sternotomy approach is favored by most centers in the United States.

In performing the procedure via thoracotomy, the chest is usually entered through the fourth intercostal space. The lung is retracted inferiorly and medially and the mediastinal pleura opened posterior to the SVC. The innominate and/or subclavian arteries are dissected free from the surrounding tissues and controlled with vessel loops. During this portion of the dissection, great care is taken to avoid the recurrent laryngeal nerve, which, on the right side, courses around the distal innominate artery at its bifurcation into subclavian and common carotid arteries. Next, the PA is mobilized, first proximally toward the pericardial reflection and then distally to the first bifurcation. The vessels are controlled with vascular tapes. An expanded polytetrafluoroethylene (ePTFE, Gore-Tex) graft is then beveled with scissors to conform to the natural curve of the systemic artery. A Cooley or Castaneda vascular clamp is applied to the innominate artery, encompassing the origin of the right subclavian artery and an arteriotomy is made on the inferior aspect of the artery. The anastomosis is performed with a 7-0 monofilament suture in a running fashion. Some authors prefer systemic heparinization prior to systemic vessel clamping; we prefer to heparinize the patient after the first anastomosis is complete. The clamp is then repositioned on the graft to minimize systemic arterial trauma. If at this point the azygos vein lies in the direct path of the shunt, it is ligated and divided. The distal anastomosis is performed by first placing a stay suture in the direct center of the superior margin of the unmanipulated PA to make sure that there will be no torsion or kinking during occlusion. Prior to initiating the anastomosis, vascular tapes are used for a test-occlusion of the PA. Once the surgeon is assured that the patient will tolerate single-lung perfusion, the pulmonary arteriotomy is made by excising a circular portion of the PA. The excised portion should be larger than the diameter of the graft so as to avoid proximal stenosis. The graft is then cut to length, attempting to avoid any redundancy. The anastomosis is again performed with a 7-0 monofilament suture in a running fashion. Clamps and tapes are then released, hemostasis is assured, and the chest closed with a pleural drain. There should be a nearly instantaneous increase in the patient's oxygen saturation and a drop in the diastolic blood pressure, with a palpable thrill in both shunt and PA.

If a sternotomy is chosen, the sequence remains the same. Following sternotomy and thymectomy, the pericardium is left undisturbed and the innominate artery is mobilized to the bifurcation. A limited pericardial incision is then made in order to mobilize the PA between the aorta and SVC. The anastomosis is performed as described above. Ligation of the ductus arteriosus or additional sources of pulmonary blood flow are dependent upon individual patient anatomy as well as surgeon's preference.

The size and the length of the shunt are important factors in controlling the amount of pulmonary blood flow. Decisions regarding shunt dimensions should consider both the size of the patient as well as whether additional sources of pulmonary blood flow exist. Most infants of normal birth weight require a 3.5-mm shunt. Infants weighing less than 3.5 kg should be treated with a shunt of no less than 3 mm, and the distal anastomosis should be constructed almost entirely to the subclavian artery rather than to the innominate artery. Larger infants may receive shunts as large as 4 or 5 mm. Ideal shunt characteristics may be achieved by indexing shunt diameter to the patient's body size or surface area.[8,9]

Regardless of the approach used to create the shunt, it is usually relatively straightforward to take down a modified Blalock–Taussig shunt through a median sternotomy at the time of the next procedure. A right-sided shunt can be found by dissecting the plane between the aorta and SVC. A left-sided shunt presents more difficulty at the time of takedown and is usually identified by dissecting along the left PA, the inferior aspect of the aorta, or by entering the pleural space. The ePTFE graft can be interrupted with hemoclips and simply divided, usually with the proximal end oversewn. The distal (PA) end of the graft does not need to be removed unless access to the PA is required as part of the procedure (e.g., in case of a superior cavopulmonary anastomosis or a pulmonary arterioplasty).

## Right Ventricle-to-Pulmonary Artery Conduit

In selected diseases (hypoplastic left heart syndrome (HLHS) and pulmonary atresia with ventricular septal defect (VSD)),[10] a right ventricle-to-pulmonary artery (RV–PA) conduit can be utilized to provide pulmonary blood flow during initial palliation. The RV–PA PA conduit, first utilized in patients with HLHS by Norwood in 1981 in 4 consecutive patients, consisted of large nonvalved PTFE tubes (8 and 12 mm).[11] This was quickly abandoned due to uniformly fatal outcome of the 4 patients. Despite these initial failures, however, the concept of a RV–PA conduit has theoretical advantages over a standard systemic-to-PA shunt.[12–14] First, pulmonary blood flow occurs only during ventricular systole, and therefore diastolic runoff and "coronary steal" are eliminated. Second, because of the reduced pulmonary blood flow relative to a systemic-to-PA shunt, volume load on the ventricle is also reduced, which is critically important for single ventricle patients. Postoperative fluctuations in pulmonary and systemic vascular resistance in the single ventricle patients become less critical to control as myocardial perfusion is decoupled. However, there are also disadvantages to the RV–PA conduit. Construction of this shunt requires a ventriculotomy, which could predispose to ventricular dysfunction or enhance the substrate for late arrhythmias. Furthermore, the reduction in pulmonary blood flow could lead to reduced

growth of the branch PAs or lead to early cyanosis, necessitating earlier creation of additional sources of pulmonary blood flow (e.g., bidirectional cavopulmonary anastomosis).

Creation of the RV–PA conduit has been described by others.[11–14] Our current preference is as follows: After median sternotomy, a patch of autologous pericardium is harvested and fixed in glutaraldehyde. On the back table, a "skirt" of pericardium is created by punching a calibrated hole in the pericardial patch the exact size as the intended shunt diameter, and anastomosing the pericardium to the intended distal (PA) end of the ePTFE ringed graft using 6-0 Goretex suture. If the RV–PA shunt is performed as part of a modified Norwood operation, cardiopulmonary bypass is initiated and the pericardial skirt is created during systemic cooling. Otherwise, cardiopulmonary bypass is initiated following "skirt" creation. A 5-mm (for infants greater than 3.5 kg) or 6-mm ringed ePTFE graft is selected and the proximal end is beveled for later anastomosis to the right ventricle. Following cardiopulmonary bypass, the ductus arteriosus is ligated, the aorta is cross-clamped and the heart is arrested with a single dose of cardioplegia infused into the aortic root. The PA confluence and branch PAs are widely mobilized and encircled with vessel loops. The RV–PA shunt is most easily constructed slightly to the left side of the PA confluence. The PA is incised sharply and a small oval excised. In the case of a modified Norwood, the PA has been transected and thus a large defect already exists in which to construct the anastomosis. The cuffed PTFE graft is anastomosed to the PA with running 7-0 prolene. The vessel loops are released, and the graft is de-aired and controlled with a straight vascular clamp. Most rings are removed from the proximal aspect of the graft. A right ventriculotomy is created approximately 1.5 to 2.0 cm below the pulmonary valve using a calibrated punch. Care is taken to avoid any conal arterial branches that may be crossing the infundibulum. A small rim of endomyocardium is excised to prevent any late dynamic or muscular obstruction. The beveled end of the ePTFE graft is sutured to the edges of the ventriculotomy using interrupted pledgeted mattress sutures. Alternatively, we have utilized a running suture technique with two long homograft pledgets surrounding the ventriculotomy.

Outcomes of the RV–PA conduit have been extensively studied.[9,11,13] Many studies, including a large cohort of patients studied through Fontan completion from the Children's Hospital of Philadelphia[15] have found no difference in morbidity and mortality depending on whether a modified Blalock–Taussig or RV–PA conduit was utilized as part of first stage palliation. In the recently completed single ventricle reconstruction trial, prospectively randomized infants with HLHS received either a modified Blalock–Taussig shunt ($N = 275$) or an RV–PA conduit ($N = 274$). The trial demonstrated a 1-year transplantation free survival advantage in the RV–PA shunt group (74 percent) compared to the modified Blalock–Taussig shunt group (64 percent; $P = 0.01$).[14] However, transplantation-free survival was equivalent between both groups at a mean follow-up of 32 ± 11 months. The RV–PA conduit group had more unintended interventions and complications compared to the modified Blalock–Taussig shunt group. Importantly, pulmonary arterial size, as assessed by the Nakata Index, was lower for the RV–PA shunt group, but right ventricular size and function at the age of 14 months was similar among both groups.

## Waterston and Potts Shunts

The success of Blalock–Taussig procedure spawned a number of other systemic shunts. In 1946, Potts described an aortopulmonary shunt,[16] performed by creating an anastomosis between the descending aorta and the left PA through a left thoracotomy in patients with a right-sided aortic arch. To facilitate this procedure, a special partial occluding clamp was devised to minimize the risk of paraplegia. The Potts shunt was used throughout the 1940s and 1950s in patients thought to be too small for a classic Blalock–Taussig shunt. The Potts shunt was associated with several serious complications, including PA aneurysms and sizing difficulties, which often led to persistent cyanosis or chronic pulmonary hypertensive changes. In time, the Potts shunt was abandoned owing to its unnecessary difficulty and the risk associated with shunt takedown. Simple ligation of the shunt often leads to uncontrollable hemorrhage, requiring peripheral bypass and circulatory arrest to achieve control and repair.

In 1955 Davidson and colleagues first described a shunt between the ascending aorta and the PA. In 1962, Waterston reported a similar intrapericardial anastomosis between the posterior ascending aorta and the right PA (Fig. 62-3).[17] The procedure was performed through a right thoracotomy; the right PA and ascending aorta are both partially occluded

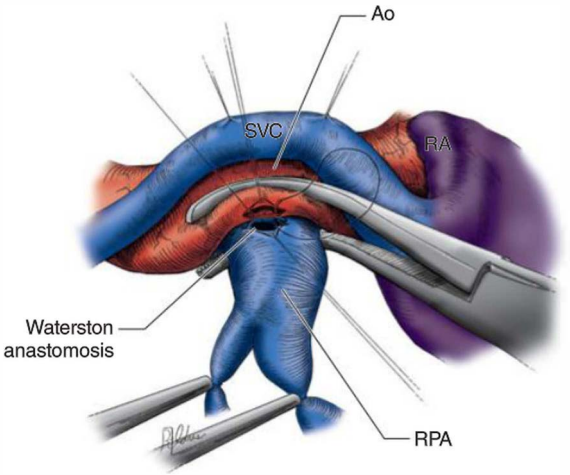



**FIGURE 62-3** Waterston shunt. Side-to-side anastomosis between the ascending aorta and right branch pulmonary artery. Ao, ascending aorta; RA, right atrium; RPA, right pulmonary artery; SVC, superior vena cava. (From Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007. With permission.)

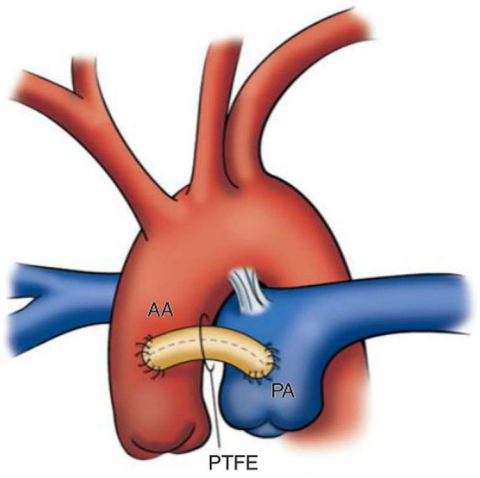



**FIGURE 62-4** Central shunt. AA, ascending aorta; PA, pulmonary artery; PTFE, polytetrafluoroethylene shunt.

with the same clamp. After making two opposing arteriotomies, the PA and ascending aorta were sewn side to side. This shunt was very effective in infants but was prone to PA kinking, with resultant unequal pulmonary blood flow and subsequent hypoplasia of the underperfused PA. The Waterston shunt is taken down intrapericardially at the time of definitive repair, the aorta is primarily closed, and the PA is patched.

In performing both the Waterston and Potts shunts, notorious difficulty was found in estimating the correct size that would prevent pulmonary hypertension or cyanosis. These shunts have been replaced by the central shunt (Fig. 62-4).

The central shunt is a modification of the Potts and Waterston shunts, created with an interposition ePTFE graft. These shunts are most often used when head vessel anatomy is unsuitable or when branch PAs are small, in the hope of encouraging pulmonary arterial growth. A small-caliber graft is preferable when creating a central shunt to avoid the potential for pulmonary overcirculation.

All systemic-to-PA shunts are designed to enhance pulmonary blood flow, but they also result in greater pulmonary venous return with subsequent left ventricular volume overload and increase in left ventricular end-diastolic dimension. In general, it is necessary to replace the systemic arterial inflow with a venous source at around 6 months of age in patients with single ventricle and by 2 years in patients with well-balanced ventricular chambers.

## PULMONARY ARTERY BANDING

First conceived by Muller and Dammann in 1952, PA banding (Fig. 62-5) was the only treatment for complex congenital heart disease with unrestricted pulmonary perfusion

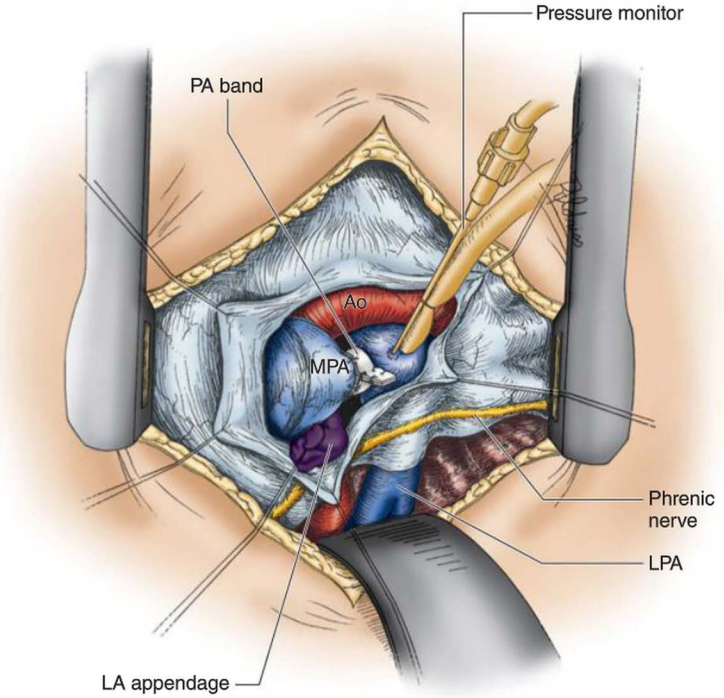



**FIGURE 62-5** Pulmonary artery band. Seen through a left thoracotomy, with a pressure monitoring line inserted in the distal main pulmonary artery. Ao, aorta; LA, left atrial artery; LPA, left pulmonary artery; MPA, main pulmonary artery; PA, pulmonary artery. (From Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007. With permission.)

(large left-to-right shunt or single ventricle with unrestrictive pulmonary blood flow).[18] For many years, the PAB was the procedure of choice for large VSDs, atrioventricular canal, or truncus arteriosus. Though effective at limiting pulmonary blood flow, PAB has largely been abandoned in the aforementioned diagnoses except in the presence of specific circumstances (e.g., small, preterm infants) because of the success of early corrective surgery. However, the development of the Hybrid approach to HLHS,[19,20] in which the ductus arteriosus is stented and the bilateral branch PAs are banded, has created a new indication for this procedure.

In addition, a few congenital lesions still lend themselves to primary palliation with PAB.[21,22] Current indications for PA banding include "Swiss cheese" VSDs, multiple VSDs with coarctation, unbalanced atrioventricular septal defects in small patients, single-ventricle lesions, and to prepare the systemic ventricle for the arterial switch operation in cases with intact septum and late presentation or for patients who have undergone atrial switch and experience systemic ventricular dysfunction. In most cases, the goal of PAB is to protect the pulmonary vascular bed from systemic or near systemic pressures associated with these lesions and to facilitate future venoarterial shunts or delayed complete repair.

The presence of a concurrent illness in a patient with an otherwise correctable lesion would also be an acceptable reason for PAB placement. Patients with pulmonary overcirculation are more prone to respiratory illness and have less reserve to cope with viral illnesses such as pneumonia due to the respiratory syncytial virus (RSV). This disease state can last for weeks, often with the need for prolonged mechanical ventilation as the lungs recover; PAB in the short term may allow for the child to improve and have the lesion corrected in a better clinical condition.

Except in cases of aortic coarctation associated with a VSD not suitable for simultaneous repair, PAB is usually approached by most surgeons via a median sternotomy. After partial thymectomy, the pericardium is opened from the base of the innominate artery to the level of the pulmonary annulus. Pericardial stay sutures are placed to enhance exposure. The aorta and PA are carefully separated with cautery, and the PA is then encircled with careful blunt dissection. It is crucial to do as little vertical dissection between the aorta and PA as possible so as to minimize band migration. Although some authors recommend Teflon-impregnated Dacron, we use a 3.0-mm ePTFE conduit to create the band. We prefer this technique because the ePTFE band causes less of an inflammatory response and can usually be removed off bypass without any further intervention on the debanded PA if the PAB has been in place for less than 6 months. In addition, we have found that, when a VSD closes spontaneously during the period that the band is applied, the band can be removed in the cardiac catheterization laboratory by balloon dilatation, thus avoiding resternotomy. Bands constructed of either Teflon, silk or Dacron will often require a period of cardiopulmonary bypass with PA reconstruction in order to remove the band.

The banding material is advanced around the PA. The band is sequentially tightened using small Weck clips until the band is fixed to the desired circumference. In 1972, Mustard and Trusler introduced a formula to estimate the size of the band needed in patients with VSDs.[23] This formula suggested that the circumference of the band in millimeters should be equal to the child's weight in kilograms plus 20. This formula may be helpful as a guideline; however, intraoperative pressure measurements should be used to individualize the band size for each patient. The distal pulmonary arterial pressure should be reduced to somewhere between one-third and one-half of systemic, and systemic arterial saturations should remain between 75 and 85 percent on 50 percent inspired oxygen. The systemic pressure will usually increase by 10 to 15 mm Hg after proper banding.

Several complications are specific to PA banding. Improper band sizing can produce pulmonary under- or overcirculation with resulting congestive heart failure or cyanosis from excessive right-to-left shunting. However, this is an unusual problem if intraoperative pressures are taken correctly. Another possible complication is band migration. This problem may lead to impingement on the PA bifurcation, causing stenosis of one or both branch PAs. It is most common for the right PA to be compromised during banding, producing left PA hypertension and right PA ostial stenosis. Banding of the PA has been also associated with injury to the left phrenic nerve at the time of PAB placement or reentry. This is, of course, particularly detrimental in patients with functionally single ventricle staged toward Fontan-type physiology. Lastly, in palliating single-ventricle lesions with a posteriorly displaced conal septum, banding is thought to contribute to obstruction of left ventricular outflow tract.

## SYSTEMIC VENOUS–PULMONARY ARTERIAL SHUNTS

The goal of a systemic venous-to-PA shunt is to improve oxygenation by channeling the systemic venous return in part or in whole to the pulmonary vasculature. This procedure is commonly used in patients with a cyanotic defect who are staged to a Fontan circulation or total cavopulmonary connection (see Chapter 77). Although first performed experimentally and reported in 1950 by Carlon,[24] William Glenn is credited with the clinical application of a systemic venous-to-PA connection, effectively bypassing the right ventricle.[25] The initial ("classic") shunt developed by Glenn was an end-to-end anastomosis, in which the distal end of the transected SVC was sutured to the distal end of the right PA. The original Glenn shunt (Fig. 62-6) was later replaced by the bidirectional Glenn cavo-pulmonary anastomosis (Fig. 62-7), a modification in which an end-to-side PA anastomosis is created by suturing the distal end of the transected SVC to the intact right PA, thus providing a conduit for bidirectional flow to both branch PAs.[26] The bidirectional Glenn provides a reliable source of pulmonary blood flow and relieves the volume overload on the ventricle imposed by systemic-to-PA shunts. Furthermore, it unloads the right ventricle in cases of right ventricular hypoplasia and Ebstein's malformation

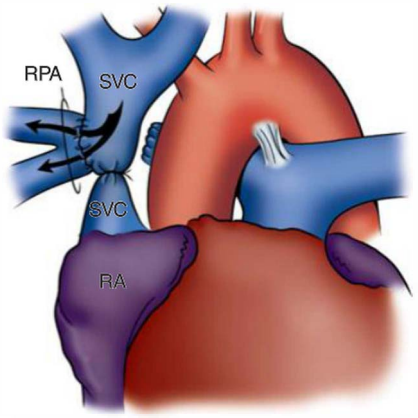



**FIGURE 62-6** Classic Glenn superior cavopulmonary connection. RA, right atrium; RPA, right pulmonary artery; SVC, superior vena cava.

of the tricuspid valve (see Chapters 70 and 85). The major limitation to early palliation with a Glenn-type anastomosis is the need for low pressures in the pulmonary bed, which are usually not present until 3 or 4 months of age.

Although initially successful, the Glenn shunt fell out of favor as the final procedure when the Fontan or total caval pulmonary connection was popularized for patients with single-ventricle physiology. Conversion of the Glenn anastomosis to a total cavopulmonary connection allowed complete separation of the systemic and pulmonary circulations, completely obviated the volume load on the single ventricle, and also reduced the development of pulmonary arteriovenous malformations by providing inferior vena cava blood to the lungs. Results from the Kawashima operation for patients with interrupted inferior vena cava with azygous continuation, in which only the hepatic venous effluent is excluded from the cavopulmonary connection, suggested the presence of an incompletely defined "hepatic factor" within the IVC effluent that reduces development of pulmonary arteriovenous malformations.[27] Subsequent studies, in which the hepatic venous blood is redirected to the pulmonary circulation with resolution of the arteriovenous malformations, have supported this concept.[28,29] Although a trend toward early completion of a total cavopulmonary connection (at less than 2 years of age) has been established, not all children are ideal candidates for immediate bicaval connection to the PA. In these patients, a bidirectional Glenn became an intermediate step in management of the single ventricle. The usual palliative sequence for univentricular heart disease is therefore the creation of a systemic-to-pulmonary shunt (or placement of a PAB in cases with pulmonary overcirculation) for palliation in the neonatal period, followed by a Glenn or hemi-Fontan (see Chapters 76 and 77) connection at around 6 months of age and, eventually, by completion of the Fontan operation when the child reaches about 15 kg in size.

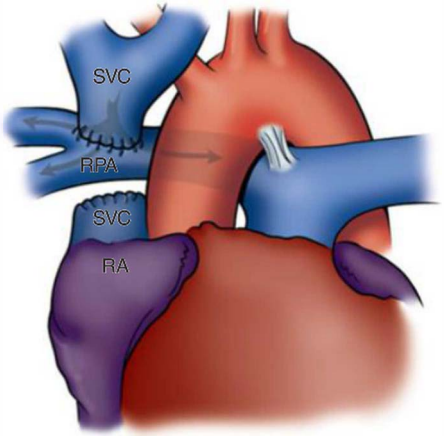



**FIGURE 62-7** Bidirectional Glenn cavopulmonary anastomosis. RA, right atrium; RPA, right pulmonary artery; SVC, superior vena cava.

Following sternotomy, sharp dissection is undertaken to gain control of the systemic-to-pulmonary shunt, or, if present, the PAB is dealt with. Next, the right PA and SVC are fully mobilized. The azygous vein is also dissected free and is ligated and optionally divided for added mobility. Stay sutures are placed in the lateral extent of the SVC and the exact midpoint of the superior portion of the PA to avoid distortion during clamping. The patient is then systemically heparinized. Cardiopulmonary bypass is initiated with ascending aortic cannulation and venous cannulation. Two venous cannulae are required, one placed in the very proximal SVC or innominate vein and the other placed either at the inferior atriocaval junction (if a concomitant transatrial procedure is required) or through the right atrial appendage. Alternatively, a shunt can be utilized between SVC a nd right atrium, while in rare instances (when redundant blood flow to the pulmonary vasculature exists) the procedure can be performed by avoiding shunting or cardiopulmonary bypass altogether.

As bypass is instituted and the systemic-to-pulmonary shunt is ligated, the cardiac portion of the SVC is cross-clamped, divided, and oversewn with great care not to injure the sinus node. In the case of a previous Blalock–Taussig shunt, the graft-to-PA anastomosis is taken down and the arteriotomy widened so that the caliber is larger than that of the SVC. The anastomosis is performed in a running fashion using 7-0 monofilament suture, taking care to avoid purse-stringing of the suture line. In cases where purse-stringing appears likely, intermittent locking sutures or interrupted sutures may prove useful. This portion of the procedure is usually performed at normothermia with the heart beating. Cardioplegic or fibrillatory arrest may be necessary if an atrial septectomy or tricuspid valve repair is required. At the conclusion of bypass, it is important to monitor both SVC pressure and arterial oxygen saturation. In cases in which the arterial saturation is intolerably low or the SVC pressure is significantly elevated, a technical problem should be considered. If no technical error can be identified and the arterial saturation is unresponsive to ventilatory or pharmacologic manipulation, placement of a small additional systemic-to-pulmonary shunt may be considered. Postoperative

anticoagulation is a controversial subject, but most authors usually recommend at least the use of antiaggregant therapy.

The Glenn shunt has a reported operative mortality of 4 to 5 percent and can sustain palliation for 5 to 7 years.[30] Patients normally maintain saturations in the low to mid 80s, which generally persist to the fourth year of life, when cyanosis becomes symptomatic. A well-known complication of the superior cavopulmonary connection is the development of pulmonary arteriovenous malformations as discussed previously, or venovenous collaterals (superior-to-inferior vena cava) which result in shunting of the upper body venous return away from the PA to the right atrium and hence accelerated cyanosis. Once cyanosis progresses or the patient reaches approximately 2 years of age, the patient should undergo evaluation for completion of the total cavopulmonary connection.

## ATRIAL SEPTECTOMY AND SEPTOSTOMY

For some lesions, palliation can be provided by increasing the intracardiac mixing of venous and arterial blood. This can be accomplished either through a surgical atrial septectomy or a percutaneous balloon or blade septostomy. There are various ways of performing a surgical septectomy without cardiopulmonary bypass. The Blalock–Hanlon septectomy was first performed in 1950 through a right thoracotomy.[31] The right and left atrium are occluded with a single clamp. The atria are opened within the clamp with two parallel incisions (on either side of the septum); a portion of the atrial septum is then grasped and excised. The clamp is repositioned to allow the septum to fall back into the atria, and the resulting common atriotomy is then closed. With very few exceptions, this difficult and often high-risk procedure is no longer performed. Another technique for performing a surgical septectomy is that of inflow occlusion. This is usually performed through a median sternotomy. To perform this operation, the SVC and the inferior vena cava are both encircled with a heavy tie, which can be snared. A large purse-string suture is placed in the right atrial appendage and the patient is placed in the head-down position. Both cavae are then snared and the heart beats for about 5 to 10 seconds, at which time the aorta is cross-clamped. The right atrium is opened within the boundary of the large purse-string suture. The tissue in the fossa ovalis is then excised. With the purse-string suture still open, the cavae are unsnared and the right atrium fills with blood and de-airs the heart. The purse-string suture in the atrium is closed and the aorta is unclamped. The whole procedure should take less than 60 seconds of cross-clamping.

Most patients who now require creation of an atrial septal defect (e.g., transposition of the great arteries without VSD) undergo a Rashkind balloon septostomy. The procedure is usually performed under either fluoroscopic or echocardiographic guidance.[32] The septostomy itself is accomplished by passing a balloon-tipped catheter via the femoral vein across the restrictive foramen ovale. The balloon is inflated and rapidly pulled back. Because the procedure is performed with an imaging study, the effectiveness of the shunt can be assessed immediately, and the septostomy can be repeated if the result is suboptimal. In patients with a thick atrial septum recalcitrant to balloon septostomy, a blade septostomy or surgical atrial septectomy can be alternatively performed.[33,34]

## SUMMARY

Despite the current trend to perform early correction of most cardiac lesions, palliative procedures remain important tools in the armamentarium of the congenital heart surgeon. These operations are designed to alter pulmonary blood flow, augment intracardiac mixing, or rehabilitate a downregulated ventricle. In some cases, several procedures are performed in sequence as part of a multistage palliation strategy or with the aim of delaying complete intracardiac repair. Each of these procedures is associated with drawbacks and specific complications, making complete repair of malformed hearts with well-balanced ventricles ideal whenever possible.

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## PALLIATIVE OPERATIONS FOR CONGENITAL HEART DISEASE BOARD REVIEW QUESTIONS (CHAPTER 62)

1. Palliative options for a 5-day-old neonate who weighs 3.5 kg with ductal-dependent pulmonary blood flow include all of the following EXCEPT:

   A. Modified 3.5-mm Blalock–Taussig shunt
   B. 5-mm RV–PA shunt
   C. Superior cavopulmonary shunt
   D. Modified 4.0-mm Blalock–Taussig shunt
   E. Ductal stent

2. For a 2.8-kg infant with multiple Swiss-cheese VSDs, the optimum circumference of a main PAB would be:

   A. 5 mm
   B. 12 mm
   C. 15 mm
   D. 20 mm
   E. 23 mm

3. The Waterston shunt involves an anastomosis between the:

   A. Right PA and the SVC
   B. Right PA and the innominate artery
   C. Left PA and the descending aorta
   D. Right PA and the ascending aorta
   E. Left PA and the left subclavian artery

4. A 4.0-kg neonate with tricuspid atresia, Type 1a is undergoing a modified Blalock–Taussig shunt using a 4.0-mm conduit and concomitant ligation of the ductus arteriosus through a sternotomy. Which of the following is the LEAST likely complication?

   A. Right recurrent laryngeal nerve injury
   B. Subsequent right PA stenosis
   C. Shunt thrombosis
   D. Pulmonary overcirculation
   E. Seroma formation

5. A 5.7-kg infant who is status post a right modified Blalock–Taussig shunt for pulmonary atresia with intact ventricular septum without right ventricular-dependent coronary circulation is undergoing conversion to a bidirectional Glenn shunt. The patient is cannulated for cardiopulmonary bypass, yet upon commencement of bypass, the perfusion pressure is persistently low and there is tremendous left heart return. The best next course of action to correct the situation would be:

   A. Do the repair off bypass to avoid further myocardial injury from ventricular unloading.
   B. Ligate the existing Blalock–Taussig shunt.
   C. Place a common atrial vent to avoid distension and augment drainage.
   D. Give additional phenylephrine in the circuit to augment systemic perfusion pressure.
   E. Perform the repair under deep hypothermic circulatory arrest.

## ANSWERS

1. **Answer C.** A neonate with ductal-dependent pulmonary blood flow requires establishment of a controlled source of pulmonary blood flow before closure of the native ductus arteriosus. Creation of a surgical systemic-to-PA shunt or stenting of the ductus arteriosus are suitable

options for this patient. Neonates are not candidates for a superior cavopulmonary anastomosis owing to their relatively high pulmonary vascular resistance, which would severely impede the passive drainage required from a systemic venous–pulmonary anastomosis.

2. **Answer E.** Although guided by intraoperative measurements of distal PA pressure, the gradient across the band, and the estimated right ventricular pressure, Trusler's rule provides a good estimate of the ideal band circumference. The Trusler's formula for VSD is the child's weight in kilograms + 20, which would be approximately 23 mm in this scenario. The distal pulmonary arterial pressure should be reduced to somewhere between one-third and one-half of systemic, and systemic arterial saturations should remain between 75 and 85 percent on 50 percent inspired oxygen. The systemic pressure will usually increase by 10 to 15 mm Hg after proper banding.
3. **Answer D.** The Waterston shunt is a central shunt, and involves creation of an anastomosis between the right PA and the posterior ascending aorta through a right thoracotomy.
4. **Answer D.** A 4.0-kg neonate with type 1a tricuspid atresia (concomitant pulmonary atresia) has ductal-dependent pulmonary blood flow. A 4.0-kg neonate would require at least a 4.0-mm shunt to avoid early development of cyanosis. If the ductus was ligated at the time of systemic-to-PA shunt creation, the shunt would become the sole source of pulmonary blood flow and would be unlikely to develop thrombosis. All of the other listed complications are possible sequelae of any modified right Blalock–Taussig shunt placed through a median sternotomy.
5. **Answer B.** Patients with systemic-to-PA shunts must have their shunt controlled at the institution of cardiopulmonary bypass to avoid "steal" into the pulmonary circulation. Patent shunts will lead to inadequate systemic perfusion pressures unless excessively high flows are maintained via the bypass circuit. In addition, though not a concern for a bidirectional Glenn, copious left heart return from a patent shunt will also impede visualization of intracardiac repairs.

63

# Patent Ductus Arteriosus

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**KEY CONCEPTS**

- Epidemiology
  - The ductus arteriosus is a normal fetal structure, that arises from the left sixth aortic arch, and connects the proximal left main pulmonary artery to the upper descending thoracic aorta. Persistent patency beyond the neonatal period occurs in approximately 1 in 2500 term live births, with a male-to-female ratio of 2:1. Patent ductus arteriosus (PDA) accounts for 5 to 10 percent of all congenital heart defects, with up to 30 percent of cases observed in preterm infants.
- Pathophysiology
  - The presence of a large, nonrestrictive PDA leads to left-to-right shunting with pulmonary overcirculation, subsequent left atrial dilatation, left ventricular volume overload, and congestive heart failure; if left untreated, irreversible pulmonary hypertension and Eisenmenger physiology with right-to-left shunting and cyanosis ultimately ensue.
- Clinical features
  - Presentation may range from absence of symptoms to the presence of a "machinery-like" murmur with poor feeding, failure to thrive, tachypnea, and recurrent respiratory infections.
- Diagnosis
  - Chest x-ray typically discloses increased pulmonary vascular markings, pulmonary edema, and cardiomegaly. Transthoracic echocardiography demonstrates the ductal anatomy and any coexisting defects.
- Treatment
  - Treatment strategies include pharmacologic closure with indomethacin in premature infants, catheter-based closure with coil occlusion in older children and adults, video-assisted thoracoscopic (VATS) closure, and conventional thoracotomy and ligation. Whereas operative outcomes in premature newborns are heavily dependent on associated comorbidities, morbidity and mortality from surgical or percutaneous closure in infants and children are almost negligible.

## INTRODUCTION

The ductus arteriosus is a normal vascular connection between the pulmonary arterial trunk and the proximal descending thoracic aorta, and is an essential component of the fetal circulation. During fetal life, it allows right-to-left shunting of maternally-derived oxygenated placental blood to the systemic circulation, bypassing the high-resistance pulmonary bed. Following birth, increases in oxygen tension and a drop in pulmonary vascular resistance trigger spontaneous closure (contraction and subsequent fibrosis) of the ductus. Patent ductus arteriosus (PDA) is the persistence of the ductus as a vascular structure (rather than a ligamentous connection) beyond the early neonatal period, leading to unabated left-to-right shunting between the aorta and pulmonary artery with subsequent pulmonary overcirculation.

With an incidence of 1 in 2500 to 5000 births, PDA is the second most common congenital cardiac malformation.[1] Although recognition of the presence of the ductus arteriosus during fetal circulation dates to Galen, it was not until 1907 that John Monro first suggested surgical ligation of PDA in an address to the Philadelphia Academy of Surgery.[2] Thirty-one years later, in 1938, the first operation was attempted by Graybiel and Stieder in a 22-year-old woman with bacterial endocarditis involving the arterial duct.[3] Although the PDA was successfully ligated, the patient succumbed to infection and gastrointestinal complications a week later. Although primacy is still disputed, Robert Gross is credited, later in that same year, with the first ligation of a PDA in a 7-year-old

child with severe heart failure.[4] Although a PDA can today be interrupted through interventional or minimally invasive techniques, operative ligation remains a model of finest surgical practice: predictable anatomy, minimal morbidity, and excellent outcomes.

## ANATOMY AND EMBRYOLOGY

Early in fetal development, the aortic sac is connected to paired dorsal aortae through six arterial arches (see Chapter 84).[5,6] The normal ductus arteriosus develops from the dorsal portion of the left sixth arch. However, because of the bilateral symmetry of the arterial system, arterial ducts can be bilateral or absent, right- or left-sided (the latter being by far the most common variant). The sixth arches develop from the plexus of capillaries that supply the developing buds. These capillaries initially arise from the aortic sac but later join the dorsal aorta. When the arterial segments separate to form the aorta and pulmonary trunk, the sixth arches remain connected to the pulmonary trunk. On the right, the dorsal sixth arch regresses, and the ventral portion becomes the proximal right pulmonary artery. On the left, the ventral sixth arch is incorporated into the main pulmonary trunk, while the dorsal portion remains to become the ductus arteriosus.

The fetal ductus arteriosus normally originates from the pulmonary trunk as a continuation of the lesser curve of the aortic arch, a few millimeters distal and opposite to the origin of the left subclavian artery. It is typically a short and wide vessel of variable length, lying posteriorly to the left main bronchus with the vagus nerve coursing anterior to it. When there is a right-sided aortic arch, the ductus usually arises from the proximal descending aorta in conjunction with the left subclavian artery. The pulmonary end of the ductus is narrower than the aortic end and is invested by the pericardial reflection, while the aortic end is invested by the parietal pleura. The length of the ductus in infancy varies between 2 and 8 mm, with the diameter ranging from 4 to 12 mm. The left recurrent laryngeal nerve branches off the vagus and encircles the inferomedial wall of the duct before ascending behind the aortic arch into the tracheoesophageal groove (Fig. 63-1).

The wall of the ductus arteriosus differs histologically from that of the adjoining aorta and pulmonary artery. Instead of the circumferential layers of elastic fibers, the media of the ductus is made up of smooth muscle cells arranged into a poorly organized spiral outer layer and a longitudinal inner layer that protrudes centrally to join the intima at "cushion" points. Large gaps between intimal cushions are filled with mucinous substance and called "mucoid lakes." The internal elastic intima is thicker than that of other vascular structures, forming wavy layers adjacent to the intimal cushions. The medial smooth muscle is particularly sensitive to $PGE_1$ and $PGI_2$, which cause, respectively, relaxation/dilatation and increased oxygen tension. The latter promotes ductal constriction.[7,8]

The first stage of ductal closure occurs within 15 to 20 hours after birth. This is triggered by a rapid decrease in plasma concentration of prostaglandins (due to loss of maternal supply) and accelerated metabolism (by increased pulmonary blood flow). In addition, increased $PaO_2$ inhibits prostaglandin synthetase, further blunting the level of circulating prostaglandins. The physiologic consequence of these changes is contraction of the smooth muscle in the ductal wall media, with subsequent thrombosis. The second stage of ductal closure is completed within 2 to 3 weeks of birth. This occurs by fibrous proliferation in the intima with necrosis of the inner layer of the media and hemorrhage into the wall. Development of neointimal mounds is stimulated by

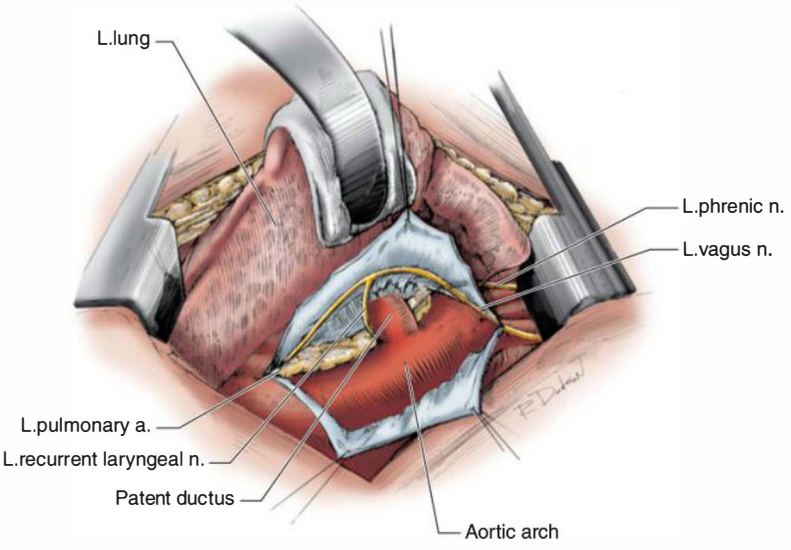



**FIGURE 63-1** Patent ductus arteriosus and contiguous structures through a left thoracotomy (surgeon's perspective). (From Castaneda AR, Jonas RA, Mayer JE, Hanley FL (eds). *Cardiac Surgery of the Neonate and Infant*. Philadelphia: Saunders, 1994:208. With permission.)

vascular endothelial growth factor. The result is the permanent sealing of the lumen and the development of a fibrous ligamentum arteriosum. The ductus is closed by 8 weeks of age in 88 percent of infants with a normal cardiovascular system. Failure of this process results in persistent patency of the ductus arteriosus. Because of the immaturity of the ductal tissue, preterm infants respond poorly to increases in oxygen tension and therefore become the patient population at highest risk of developing PDA persistence. Inability of the immature lungs to clear circulating vasodilators may also contribute to ductal persistence. The incidence of PDA increases from 7 percent in very low-birth-weight infants to as high as 42 percent in extremely low-birth-weight neonates.

## CLINICAL PRESENTATION

As pulmonary vascular resistance falls shortly after birth, increased left-to-right shunting across the PDA results in decreased systemic perfusion and a high left ventricular volume load, with decreased pulmonary compliance. The magnitude of the shunt ($Q_p$:$Q_s$) depends on the size of the ductus, as well as on the balance between systemic and pulmonary vascular resistance. In the absence of fixed pulmonary hypertension, when $Q_p$:$Q_s$ is low, the hemodynamic effect of the PDA is insignificant and physiologic derangements are minimal. With a hemodynamically significant PDA, $Q_p$:$Q_s$ is high, and increased pulmonary runoff in systole and diastole becomes detrimental to systemic pressure, leading to end-organ hypoperfusion. Furthermore, high pulmonary blood flow increases pulmonary artery pressure and, if left uncorrected, can lead to permanent pulmonary vascular disease. The clinical features of a hemodynamically significant PDA are similar to those of left-sided heart failure, with tachypnea, frequent respiratory infections, pulmonary edema, and failure to thrive. Premature infants with a PDA may present with substantial metabolic acidosis, oliguria, respiratory decompensation, and necrotizing enterocolitis.

A hemodynamically insignificant PDA may present subtly later in life. In this setting, left ventricular failure does not develop and symptoms are absent in infancy and childhood. A murmur is usually detected on routine physical examination, leading to the echocardiographic diagnosis of PDA.

A rare late mode of presentation of a PDA is infective endocarditis. The presence of a PDA may alter the local vascular immune response mechanisms or cause endothelial damage, providing a nidus for bacterial colonization. In the preantibiotics era, the average age of death in patients with a PDA surviving beyond infancy was 36 years, and infective endocarditis accounted for 45 percent of such deaths.[9]

## DIAGNOSIS

Physical examination and echocardiography represent the cornerstones for the diagnosis of PDA. The patient will present with a widened pulse pressure, a hyperactive precordium, and an occasional systolic thrill. A continuous "machinery-like" murmur radiating from the pulmonic area to the midclavicle is characteristic. Electrocardiography may demonstrate left ventricular hypertrophy and left atrial enlargement. Chest radiography may show cardiomegaly with increased pulmonary markings and enlarged pulmonary trunk. Transthoracic Doppler echocardiography is diagnostic, showing the accelerated, narrow jet flow originating from the proximal descending aorta into the left pulmonary artery (Fig. 63-2). Cardiac catheterization is currently reserved for interventional device closure after echocardiographic diagnosis. Catheterization is also indicated in the older child with a large ductus and cyanosis due to right-to-left shunting at the ductal level in order to define the reversibility of pulmonary hypertension. If pulmonary resistance is over 75 percent of systemic and is unresponsive to nitric oxide and oxygen administration, PDA closure is contraindicated.

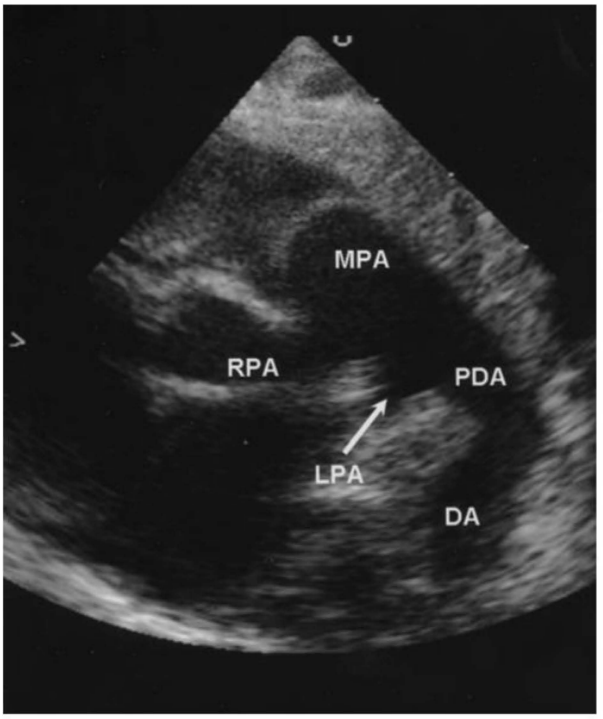



**FIGURE 63-2** Echocardiographic image of a patent ductus arteriosus from a high parasternal view. DAO, descending aorta; AI, aortic isthmus; PDA, patent ductus arteriosus. (Courtesy of William Ravekes, MD, Division of Pediatric Cardiology, The Johns Hopkins Hospital.)

## SURGICAL TREATMENT

Traditionally, the presence of a PDA is an indication for closure. With the improved sensitivity of diagnostic modalities, the very small and hemodynamically insignificant

ductus can be detected. Although likely not warranting early intervention, small PDAs can still be a potential site for bacterial endarteritis and will require monitoring.

Treatment strategies include pharmacologic closure, percutaneous closure in the catheterization laboratory, video-assisted thoracoscopic (VATS) hemoclip occlusion and conventional posterolateral thoracotomy with ligation. Percutaneous closure is effective in the treatment of children and adults with PDA. Primary surgical closure is reserved for premature newborns, small infants, and patients who have failed device closure. A randomized trial has demonstrated that early surgical ligation of PDA in neonates reduces the need for mechanical ventilation and oxygen supplementation, shortens hospital stay, and decreases the incidence of retrolental fibroplasia and necrotizing enterocolitis when compared to pharmacologic closure.[10] However, initial attempt at pharmacologic PDA closure remains the initial therapeutic modality at most institutions.

Pharmacologic treatment is successful in achieving PDA closure in up to 60 percent of premature infants.[5] A combined strategy of fluid restriction, diuretics, and indomethacin is used. Indomethacin has been utilized clinically since 1976 to facilitate ductal closure in premature infants[11] but is rarely successful in full-term neonates. Contraindications to indomethacin use in preterm infants include hyperbilirubinemia, sepsis, coagulopathy, gastrointestinal bleeding, and renal insufficiency. If indomethacin use is contraindicated or fails, surgical closure is undertaken. Preterm infants typically undergo two to three courses of indomethacin (12–24 h apart) before being considered for surgical closure.

Early operative PDA closure carries low operative morbidity and mortality. Ductal ligation is now frequently performed at the bedside in the neonatal intensive care unit in order to minimize the risks of hypothermia and transport of the critically ill neonate. Several series have in fact reported results of bedside PDA closure to be comparable to those of procedures performed in the operating room.[12] Surgical intervention in the premature infant requires close attention to maintenance of body temperature, precise ventilatory management, and fluid administration. The size and shape of the ductus can be variable. A wide, short ductus can be difficult to ligate, whereas a long, tortuous ductus is easier to interrupt. The ductal tissue in neonates tends to be extremely fragile and therefore must be handled with great caution. Care should be taken to avoid scissoring through the ductus with overaggressive ligation. A short, wide ductus may be better divided between clamps if tissue integrity is a concern. In selected cases, we prefer to gradually snare the PDA with a Goretex band, then tightened with several titanium clips. As described previously, the left recurrent laryngeal nerve makes its loop around the ductus. Care must be taken to identify and protect this nerve during surgical closure.

In the setting of a left-sided aortic arch, the patient should be positioned in the right lateral decubitus position with the left arm supported over the head to elevate the scapula. The chest is entered through a left posterolateral thoracotomy, with division of the muscular layers and entrance into the third or fourth intercostal space. The left lung is retracted anteriorly with a narrow malleable retractor, and the mediastinal pleura is incised over the descending aorta. The left recurrent laryngeal nerve should be identified and preserved. Especially in premature newborns, extensive dissection of the ductus itself should be avoided owing to the friable nature of the tissue. The left pulmonary artery, arch of the aorta, and subclavian artery should all be carefully identified (Fig. 63-2). The ductus is frequently larger than the aortic arch and isthmus. The most common technical error is the inadvertent ligation of the left pulmonary artery, which is mistaken for the ductus. The pleura is incised just above and below the ductus using fine scissors. We prefer to apply a hemoclip to close the PDA (Fig. 63-3); however, if the duct is unusually large or the patient is an older infant or child, it may be encircled with silk ties, doubly ligated, and divided. Although division is the ultimate form of interruption, it should be utilized with caution in the presence of a short, broad-based hypertensive duct or in the fragile premature newborn. Prior to ductal ligation, test-occlusion of the ductus with forceps should be performed. A rise in diastolic pressure should be noted, as well as maintained pulsatility in the descending aorta and unaltered oximetric signal in the lower extremities. A medium-sized hemoclip is applied, with the tip of the clip visible posteriorly beyond the inferior margin of the ductus. The mediastinal pleura is typically left open. A chest tube may be placed if there is concern for pulmonary parenchymal injury.

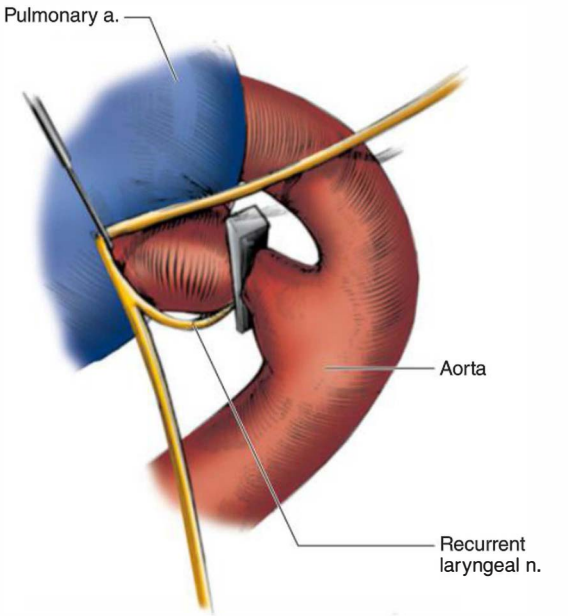



**FIGURE 63-3** A hemoclip is utilized to interrupt the patent ductus arteriosus in premature infants. (From Castaneda AR, Jonas RA, Mayer JE, Hanley FL (eds). *Cardiac Surgery of the Neonate and Infant.* Philadelphia: Saunders, 1994:209. With permission.)

Several specific considerations should be made for adults presenting with a PDA. Historical series from the 1960s suggest that 40 percent of patients with untreated PDA would die by age 45 because of chronic pulmonary vascular disease or Eisenmenger syndrome. When patients present in adulthood, diagnostic catheterization should be performed to determine operability by assessing the degree of pulmonary hypertension and responsiveness to nitric oxide and oxygen. Since adult patients may have significant calcification of the ductus, the PDA should be approached through a median sternotomy with cardiopulmonary bypass. A median sternotomy may also be useful in patients with a wide, short PDA. The transpulmonary artery approach described by Goncalves-Estella[13] with support of cardiopulmonary bypass can be used in these cases, with temporary occlusion of the branch pulmonary arteries. The aorta and the main pulmonary arterial trunk are dissected apart. Cardiopulmonary bypass is established with a single venous cannula and aortic return line, cooling is begun, and the patient is placed in the Trendelenburg position. The opening of the ductus is controlled by digital compression on the pulmonary arterial confluence, avoiding excessive pulmonary arterial runoff upon institution of corporeal circulation. When adequate systemic cooling is achieved, low-flow cardiopulmonary bypass is instituted. The pulmonary artery is opened and the incision extended onto the left pulmonary artery opposite the orifice of the PDA. The ductal opening is next closed with pledgeted mattress sutures if no calcification is present. If significant calcification of the pulmonary arterial end of the ductus is noted, the orifice should be closed using a bovine pericardial or Dacron patch. Alternatively, the duct can be controlled with a balloon-tipped catheter inserted though the pulmonary artery into the descending aorta at low-flow perfusion. In a variation of this technique, a patch can be slid over the catheter and secured in place.[14]

Aneurysmal dilatation of the arterial duct has been described, with potential risks of rupture, erosion, infection, and thromboembolism. Neonatal ductal aneurysms usually resolve spontaneously by thrombosis. Any patients above 2 months of age with a ductal aneurysm should undergo prompt surgical repair. These patients may present with hoarseness from recurrent laryngeal nerve traction, vocal cord paralysis, or obstruction of the left mainstem bronchus. Surgical treatment is performed on cardiopulmonary bypass, with aneurysmal excision and patch aortoplasty under circulatory arrest.

The first VATS PDA closure was performed in 1991 by Laborde.[15] Video-assisted closure can be performed with three to four small incisions for instrumentation. Port incisions are placed in a line to facilitate posterolateral thoracotomy extension should conversion to a conventional approach be required. This innovative approach minimizes chest wall trauma, division of muscular planes, and rib retraction.[16] The ductus is dissected free of surrounding tissues, the recurrent laryngeal nerve is identified, and the duct is interrupted with clips. Good results from VATS closure have been obtained in low-birth-weight infants. Postulated advantages are reduced patient discomfort and hospital length of stay. This technique has been used in neonates, children, and adults. In Laborde's series of 332 consecutive pediatric patients, mortality was zero, with minimal morbidity.

Closure with robotic assistance has also been performed. The limitations, however, are due to the physically large size of the instruments, requiring 7-mm ports. Current robotic systems use widely spaced operating arms, thus limiting their use to adults. No tactile feedback is available to indicate to the surgeon the degree of force applied.

Results of surgery with a traditional posterolateral thoracotomy approach have a long-standing record of providing a durable repair with minimal morbidity and mortality. In 1994, Mavroudis and coworkers reported the results of the traditional surgical approach at their institution between 1947 and 1993.[17] This series included 1108 patients who underwent ligation and division of a PDA. There were no mortalities and no recurrences. The authors concluded that these results represent the standard of care to which video-assisted and catheter-based closure should be compared. Recent series describing results with the VATS approach have shown comparable results with minimal residual shunts and no important complications.[18] Only 3 patients in a series of 300 endoscopic cases required conversion to a standard posterolateral thoracotomy, and only two experienced transient functional impairment of the recurrent laryngeal nerve.

## TRANSCATHETER OCCLUSION OF A PATENT DUCTUS ARTERIOSUS

The first nonsurgical PDA closure was reported by Porstmann in 1967.[19] Closure was accomplished by implantation of an expandable plug within the arterial duct. Although the required delivery system was much too large to be of practical use in small children, this report pointed to the possibility that repair of congenital heart defects could be accomplished by transcatheter techniques. Twelve years later, Rashkind developed a double-umbrella device to close the ductus arteriosus of a 3.5-kg infant.[20] Clinical trials met with some success, but rates of residual leakage and technical difficulties precluded wide acceptance or FDA approval of the device. In 1992, Gianturco embolization coils (Cook Inc., Bloomington, IN) were first used to produce embolization of the ductus arteriosus by modification of the technique used in the preceding decade to embolize fistulae, arteriovenous malformations, and other vascular abnormalities. Cambier and colleagues reported the first case of successful transcatheter PDA coil embolization in 1992.[21] This technique immediately gained wide popularity for its low cost, excellent safety, efficacy, and for its adaptability to a wide spectrum of patients ranging from infancy to adulthood. Coil embolization is still used to close small PDAs, but the technique can be cumbersome and the residual leak rate is higher when larger PDAs are encountered, particularly in small infants. Thus a number

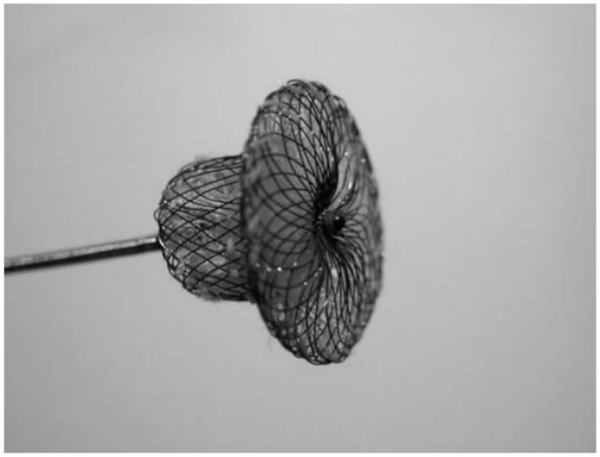


**FIGURE 63-4** Amplatzer ductal occluder (ADO) device. (Courtesy of Richard Ringel, MD, Division of Pediatric Cardiology, The Johns Hopkins University Hospital.)

of investigators have continued to work on the challenge of developing a device specifically designed to close the ductus arteriosus. In 2002 the first such device to obtain FDA approval was the Amplatzer ductal occluder (ADO); it remains to date the only device specifically approved for nonsurgical closure of the ductus arteriosus in the United States.[22] The device consists of 72 strands of nitinol wire woven into a mushroom-shaped plug with a core of polyester fiber (Fig. 63-4). It is particularly helpful for closure of moderate-to-large PDAs in patients above 6 months of age. For infants younger than 6 months, the right-angle orientation of the flat aortic retention disk to the plug portion of the device that fits within the ductus itself does not truly conform to aortic anatomy, and may protrude excessively into the aortic lumen of a smaller infant. However, a new, doubly articulated Amplatzer ductal occlude is currently in trials. It is softer, better able to mold into ductal variations and should be safer to use in smaller infants.[23] Device closure of the PDA offers the obvious advantage of avoiding a surgical incision. The procedure at most centers is performed on an outpatient basis under moderate sedation, with use of percutaneous femoral venous and arterial access (Fig. 63-5). Current contraindications to the use of nonsurgical techniques currently include a large (≥4 mm diameter) PDA in infants weighing 6 kg or less, active endocarditis, or pulmonary hypertension with right-to-left shunting through the ductus arteriosus.

Several treatment algorithms have emerged, wherein smaller PDAs (minimum diameter ≤2.5 mm) are closed by coil embolization[21,22] and larger PDAs are closed with an ADO; with this strategy, successful implantation with complete closure will approach 98 percent or greater.[23]

Complications of coil embolization are uncommon. Femoral artery thrombosis is rare and essentially seen only in smaller infants. Almost all of these problems are transient, responding to anticoagulant or thrombolytic therapy. Embolization of the coil into the pulmonary arteries is the most frequently described complication, occurring in up to 16 percent of procedures;[24] however, virtually all of these embolized coils can be removed immediately during catheterization without sequelae. Embolization into a systemic artery is very unusual, occurring in up to 3 percent of cases. Hemolysis

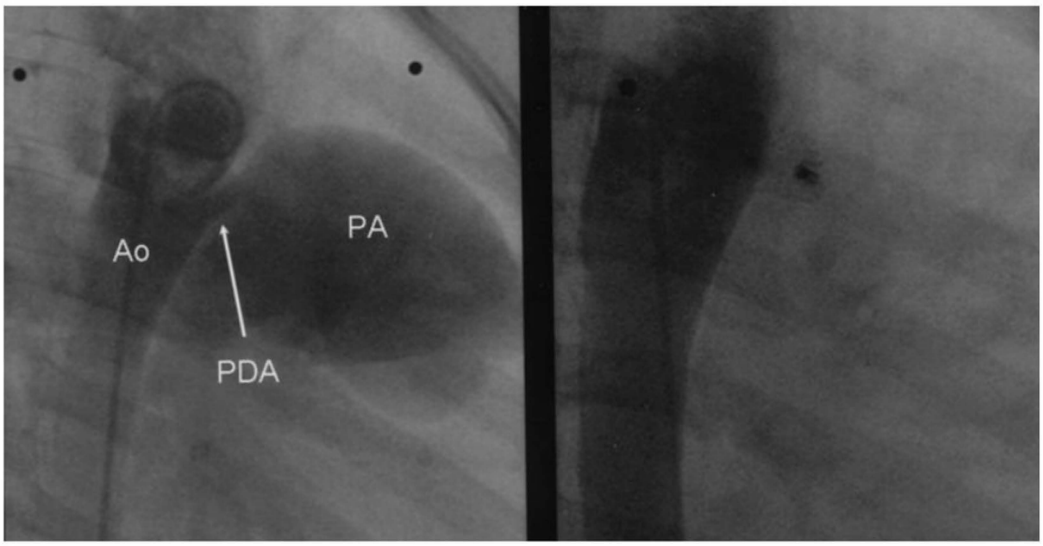



**FIGURE 63-5** Interruption of patent ductus arteriosus with Amplatzer ductal occluder (ADO) device. Left: Contrast is seen within t he ductus arteriosus with injection in the thoracic aorta. Right: Successful closure of the arterial duct. PDA, patent ductus arteriosus. (Courtesy of Richard Ringel, MD, Division of Pediatric Cardiology, The Johns Hopkins University Hospital.)

following coil embolization is very rare and can be avoided by implanting additional coils[25,26] to eliminate any residual shunting identified on the postimplant aortic contrast study. Creation of left pulmonary artery stenosis or aortic obstruction has been described infrequently, but is almost exclusively seen in the small infant with a PDA that requires three or more coils to achieve adequate closure. Complications associated with the Amplatzer device are likewise uncommon, and usually minor when use of the device is restricted to patients over 6 months of age. Major adverse events (i.e., device embolization, partial pulmonary artery obstruction, loss of femoral pulse, bleeding requiring transfusion) occurred in 10 of 439 (2.3 percent) patients during phase III FDA trials, with most of these occurring in smaller infants.[22]

## SUMMARY

Treatment of PDA can be performed with low mortality and morbidity. Multiple options are now available, ranging from medical to surgical to interventional catheter-based treatment. Nonsurgical device closure of the ductus arteriosus can be performed with a success rate of about 98 percent and a complication rate below 3 percent with the use of an interventional strategy that employs embolization coils for small PDAs and ADOs for moderate-to-large PDAs. Operative closure is recommended for infants with congestive heart failure who weigh 6 kg or less; such patients should not wait until they are of more appropriate size for a nonsurgical approach.

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## PATENT DUCTUS ARTERIOSUS BOARD REVIEW QUESTIONS (CHAPTER 63)

1. Which is true regarding embryology of the ductus arteriosus?
   A. The normal ductus arises from the right sixth arch.
   B. The arches remain connected to the pulmonary trunk when the aorta and pulmonary artery divide.
   C. The ventral portion of the right arch becomes the distal right pulmonary artery.
   D. The dorsal portion of the left arch is incorporated into the main pulmonary trunk.
   E. The ventral portion of the left arch becomes the distal left pulmonary artery.

2. Which is correct regarding closure of the ductus arteriosus?
   A. The first stage is complete within 4 to 6 h of birth.
   B. The first stage is triggered by an increase in plasma prostaglandins.

C. Increased $Paco_2$ increases prostaglandin synthetase.
D. Second-stage closure is complete by 2 to 3 weeks after birth.
E. The ductus is closed by 4 weeks in 90 percent of infants.

3. Which is true regarding treatment of a PDA?
   A. Forty percent of patients will die by age 45.
   B. The PDA should be approached through a left thoracotomy in an adult.
   C. Control of the PDA is not required prior to cardiopulmonary bypass.
   D. Neonatal ductal aneurysms require urgent surgical repair.
   E. VATS closure is not applicable to neonates.

4. Which of the following is incorrect regarding early surgical ligation of PDA?
   A. Reduced need for mechanical ventilation
   B. Reduced requirement for oxygen supplementation
   C. Extended hospital stay due to surgical recovery
   D. Decreased incidence of retrolental fibroplasia
   E. Reduced incidence of necrotizing enterocolitis

5. Which is true regarding non-surgical approaches for a PDA?
   A. Residual leak rate is higher in large PDAs treated with coil embolization.
   B. The Amplatzer device is useful only in small PDAs for children older than 6 months of age.
   C. A PDA less than 8 mm in diameter in an infant weighing less than 6 kg can be safely closed percutaneously.
   D. Pulmonary hypertension with a left-to-right shunt is a contraindication to nonsurgical closure.
   E. Embolization into the pulmonary arteries occurs in less than 5 percent.

## ANSWERS

1. **Answer: B.** The arches remain connected to the pulmonary trunk when the aorta and pulmonary artery divide. The normal ductus arises from the left sixth arch. The dorsal portion of the right arch becomes the distal right pulmonary artery and the dorsal portion of the left arch becomes the distal left pulmonary artery. The ventral portion of the left arch is incorporated into the main pulmonary trunk.
2. **Answer: D.** Second-stage closure is complete by 2 to 3 weeks after birth. The first stage is complete by 15 to 20 h after birth and is triggered by a rapid decrease in plasma prostaglandins. Increased $Paco_2$ inhibits prostaglandin synthetase. The ductus is closed in 90 percent of infants by 8 weeks.
3. **Answer: A.** Forty percent of patients will die by age 45 from irreversible pulmonary hypertension if left untreated. The PDA should be approached via sternotomy in an adult due to calcification of the ductus, and the PDA should be controlled prior to instituting cardiopulmonary bypass to prevent excessive r unoff. Neonatal ductal aneurysms almost always resolve spontaneously by thromobosis. VATS closure can be used in neonates as well as infants and adults.
4. **Answer: C.** Early surgical ligation of a PDA decreases overall hospital stay. Early ligation is also associated with a reduced incidence of all of the remaining complications.
5. **Answer: A.** Residual leak rate is higher in large PDAs treated with coil embolization. The Amplatzer device should only be used in moderate-to-large PDAs. Contraindications to nonsurgical closure include a PDA greater than 4 mm in small infants and pulmonary hypertension with a right-to-left shunt. Embolization of devices into the pulmonary arteries occurs in up to 15 percent of procedures.

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# Atrial Septal Defects and Partial Anomalous Pulmonary Venous Connection

*Dario Troise*
*Richard Ringel*
*Francesco Paolo Annecchino*

## KEY CONCEPTS

- Epidemiology
  - Atrial septal defects (ASDs) are among the most common cardiac malformations, with prevalence [including persistence of patent foramen ovale (PFO)] greater than 15 percent for the general population and, when other cardiac anomalies are present, as high as 35 to 50 percent, with slight female predominance.
- Morphology
  - Atrial septal defects can be categorized according to the area of deficient interatrial septum: Secundum-type/PFO (most common), superior/inferior sinus venosus (SV), primum defects, coronary sinus (CoS) ASDs. Partial anomalous pulmonary venous connection (PAPVC) and scimitar syndrome often occur in the setting of an ASD. Defects are variable in size: from restrictive, to unrestrictive, to virtual absence of any septal rim.
- Pathophysiology
  - Magnitude of left-to-right shunt depends on the respective compliance of right and left ventricles and on the diameter of the defect. Because of streaming of systemic venous return toward the LA, superior and inferior SV defects can present with mild cyanosis. A minority of patients with very large defects will develop pulmonary venous obstructive disease over several decades and, eventually, fixed pulmonary hypertension (PHTn) and right-to-left shunting.
- Clinical features
  - In the absence of other malformations, ASDs are rarely symptomatic in early infancy. Features of pulmonary overcirculation (dyspnea, failure to thrive, recurrent respiratory infections) are rare in early childhood. Arrhythmias or paradoxical emboli can be initial modes of presentation.
- Diagnosis
  - Physical exam (split and fixed second heart sound) and chest x-ray (CXR) (cardiomegaly, anomalous vascular markings in PAPVC) suggest the diagnosis, confirmed by transthoracic echocardiography (TTE). In equivocal cases and for PAPVC/scimitar syndrome (SS), transesophageal echocardiography (TEE), magnetic resonance imaging (MRI), and computed tomography (CT) might be utilized. Cardiac catheterization has almost no role in the diagnostic workup, except for patients with evidence of PHTn considered for surgical closure.
- Treatment
  - Surgical closure is rarely indicated in infancy, but should be performed for unrestrictive defects in preschool age and for symptomatic adults and cases of paradoxical embolization. When the anatomy is permissive, percutaneous device closure can be considered. Conventional primary or patch closure of the defect can be accomplished via a right thoracotomy or limited/full sternotomy and, in the current era, should be associated with virtually no mortality or significant morbidity.

## DEFINITION

We define an atrial septal defect (ASD) as a deficiency of any size in the atrial septum (Fig. 64-1). Although briefly mentioned in this chapter, we will not include among ASDs the patent foramen ovale (PFO); this flap-valve is bordered superiorly by the upper limbic tissue and inferiorly by the valve of the fossa ovalis, which opens only in specific circumstances, as during coughing or the Valsalva maneuver. The ostium primum (OP) defect is part of the spectrum of atrioventricular septal defects (AVSDs) and is discussed in detail in Chapter 66.

A partial anomalous pulmonary venous connection (PAPVC) is a condition presenting with variable anatomic patterns in which some but not all pulmonary venous flow lacks drainage into the left atrium (LA). This condition, characterized therefore by one or more pulmonary veins functionally draining into the right atrium (RA), may or may not be associated with an ASD. Similar considerations apply to scimitar syndrome (SS).

In this chapter, we will discuss clinical and surgical aspects that pertain to these malformations (ASD, PAPVC, and SS) and, eventually, briefly focus on current nonsurgical alternatives for ASD closure.

## HISTORICAL HIGHLIGHTS

Following the successes of surgical closed heart procedures in the 1940s, surgeons focused their attention, mainly because of its relative simplicity, on the correction of ASDs.

This pathologic condition was described as a "perforating channel in the atrial septum" by Leonardo da Vinci in 1513,[1] but it was only in the mid-1930s that the first antemortem diagnosis was made by Roesler, in his report on 62 cases of ASD found at autopsy.[2] It was only between the late 1940s and early 1950s that, with the introduction of cardiac catheterization, a definite diagnosis became possible.

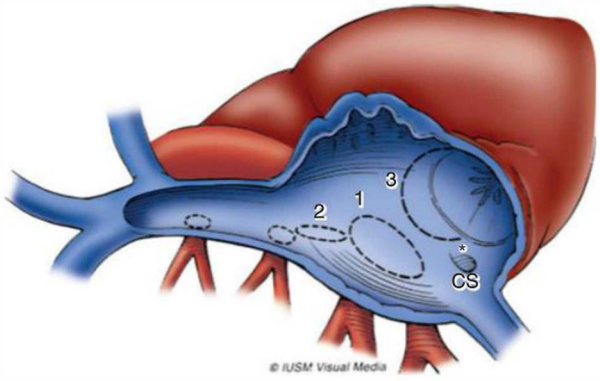



**FIGURE 64-1** Different locations of atrial septal defects as schematically seen through a right atriotomy. Along the superior vena cava, an anomalous pulmonary vein enters the systemic atrium just cephalad to the superior sinus venosus ASD (2). 1, ostium secundum ASD; 3, ostium primum ASD; CS, coronary sinus; *, location of the atrioventricular conduction system. (Copyright IUSM Visual Media.)

On account of the brief temporal mismatch between the possibility of safely diagnosing the condition during life and the feasibility of treating it surgically, three eras in the surgical treatment of the ASD can be identified: the closed-heart era, the semi-open era, and the open-heart era.

Murray was the first surgeon to report, in 1948, the closure of an ASD in a 12-year-old boy, using the external suturing technique.[3] The patient survived, but success was subtotal owing to a residual shunt, later discovered on cardiac catheterization. In the early 1950s, various closed methods were investigated, including the intussusception technique of Santy,[4] the invagination technique of Swan,[5] the digital palpation closed technique proposed by Bailey,[6] and the Sondergaard circumclusion technique.[7] All these attempts led to unacceptable mortality and a high incidence of morbidity such as atrial distortion, coronary sinus (CoS) stenosis, and the persistence of significant residual defects.

In 1953, Robert Gross utilized a semi-open technique that entailed the introduction of a cone within the atrium, allowing for closure of the defect without direct vision in the depth of a blood-filled well.[8] The cone was sutured to the atrial wall, and an atriotomy could be performed under hydrostatic pressure averting the possibility of air embolization. John Kirklin reported a series of 29 patients corrected with this technique at Mayo Clinic without operative mortality.[9]

The experiments of a short period of inflow occlusion under surface hypothermia gave way to the era of open-heart correction. Inspired by the laboratory work of Wilfred Bigelow, John Lewis at the University of Minnesota first reported successful closure of an ASD under direct vision in a 5-year-old girl.[10] Shortly thereafter, closure was accomplished with cross-circulation by C. Walton Lillehei.

With the construction of the first heart-lung machine, John Gibbon ushered the current era of open-heart surgery in the treatment of ASDs.[11]

In 1858, Peacock described for the first time the anatomic findings of a sinus venosus defect (SVD) in a 6-year-old girl who died of scarlet fever.[12] After initial approaches to PAPVC with palliative and closed techniques, Kirklin and colleagues first reported successful outcomes with open correction of various types of PAPVC.[13]

## EMBRYOLOGY

The cardiac tube is formed by an inner layer of endocardium, separated from the external myocardium by an extracellular matrix, known as cardiac jelly.[14] At the fifth week of embryonic life, the primary septum (septum primum) appears as a partition, of mesenchymal origin, in the dome of the common atrium. With further development, it occupies more space and, at the same time, incorporates two segments of mesenchymal origin that are also concomitantly forming: the endocardial cushions of the atrioventricular

canal and the vestibular spine (spina vestibuli), which originate from the dorsal mesocardium and are situated between the endocardial cushions and the anteriorly and inferiorly located septum primum. In this early phase, the space between the septum primum and the endocardial cushions is called ostium primum. It has not yet been established whether the development of the septum primum consists in growth from the roof of the common atrium toward the inferiorly displaced endocardial cushions[15] or if, as stated by Van Praagh and apparently in contrast to mainstream embryology, in an upward growth, starting from the inferior vena cava (IVC, the left wall of which is in direct continuity with the septum primum) toward the roof of the common atrium.

Before complete fusion of all mesenchymal segments of the interatrial septum, the superior part of the primary septum is reabsorbed, forming multiple fenestrations that converge into a single defect known as the ostium secundum (OS).

From the dorsal aspect of the common atrium emerges to follow an infolding of the atrial wall (septum secundum) which will be directed toward (but on the right side of) the septum primum. The plane of growth of the two septa is not identical and may thus overlap for a variable extent (Fig. 64-2). The conformation of the septum resembles that of a flap valve, in which a superoinferior plane as well as a lateral plane of growth may be identified. The development of this structure allows for half of the oxygenated placental blood to cross the interatrial communication. The septum primum becomes involved in this process, leaving vestigial remnants in the segments located in proximity of the endocardial cushions. This vestigial part, which is not overlapped by the more superior septum secundum, is the floor of the fossa ovalis. The upper edge of the flap valve does not fuse with it, but simply overlaps. With postnatal changes in heart chamber pressures, the superior edge of the fossa ovalis fuses completely (in approximately 60 percent of cases) with the lower edge of the septum secundum. Fusion is otherwise incomplete and a communication between the atria persists as a PFO.

Development of the muscular septum primum and the ventral proliferation of extracardiac mesenchyme from the dorsal mesocardium aligns the common pulmonary vein (CPV) which, once incorporated into the posterior aspect of the left-sided atrium, eventually differentiates into left and right pulmonary veins. The sinus venosus (SV) segment is that part of the atrium which, in postnatal life, will be responsible for draining systemic and coronary return as well as for the development of the smooth venous tissue between the venous ostia. The connection of the sinus with the atrial segment after the primary tube is formed is represented by the sinoatrial orifice, which, forced by the predominant development of the right-sided sinus, migrates from its midline position toward the right. The sinoatrial orifice is surrounded by venous valves on the right and left sides. Once incorporated into the dorsal aspect of the right-sided atrium, the development of the sinus segment pushes the right side of the venous valve toward a ventral line and crosses two bands that are developing perpendicular to it: the superior and the inferior limbic bands. These bands develop underneath the endocardium at the periphery of the fossa ovalis. The superior band, from the upper edge of the fossa ovalis (superior limbus of the fossa ovalis) crosses the venous valve between superior and inferior caval orifices; the inferior band (inferior limbus of the fossa ovalis), crosses the venous valve between the IVC and the CoS orifices and, eventually, forms the base of the sinus septum.

The incomplete development of the septum primum results in a defect within the fossa ovalis (Fig. 64-3). This process may be related to different mechanisms, such as incomplete overlapping of the superior limbus of the fossa ovalis (patent foramen ovale); redundancy of the foraminal valve (aneurysm of the atrial septum); partial or total breakdown of the septum primum, resulting in a single perforation of the septum primum (OS defect); or in multiple fenestrations.

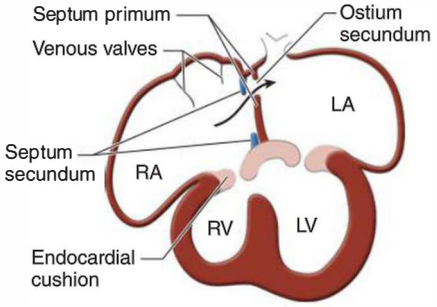



**FIGURE 64-2** Development of the interatrial septum. The atria are partitioned by the developing septum. On the left of the midline, the septum primum has obliterated the ostium primum, and is in the process of partial reabsorption in its cephalad portion (ostium secundum). The septum secundum originates from the right of the septum primum and covers the ostium secundum for a variable length. RA, right atrium, LA, left atrium, RV, right ventricle, LV, left ventricle. (Reproduced with permission from Sadler TW. Langman's Medical Embryology, 12th ed. Lippincott Williams & Wilkins; 2011)

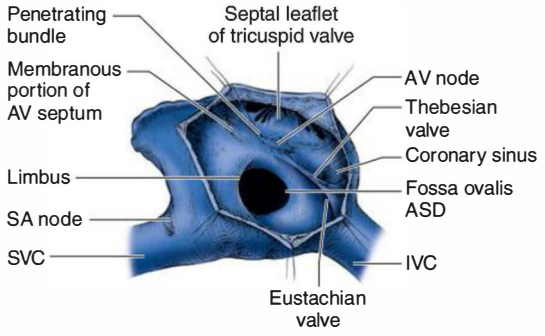



**FIGURE 64-3** Secundum-type atrial septal defect (fossa ovalis ASD). Schematic view as seen through a right atriotomy. AV, atrioventricular; IVC, inferior vena cava; SA, sinoatrial; SVC, superior vena cava. (From Kouchoukos NT, Blackstone EH, Doty DB, et al. (eds). Atrial septal defect and partial anomalous pulmonary venous connection. *Kirklin/Barratt-Boyes Cardiac Surgery*, 3rd ed. Philadelphia: Churchill-Livingstone, 2003:730. With permission.)

As previously mentioned, after maturation of the septum primum, the infolding of the dorsal common atrial cavity positions the CPV in its definitive location behind the LA. Hence, various theories have been advanced to explain the development of PAPVC. Hartley[16] suggested that the incomplete migration of the sinoatrial orifice from the midline, was the main cause of the development of a superior vena cava (SVC) medially, with displacement of the septum primum toward the septum secundum and subsequent underdevelopment of the latter. This theory would indeed account for the overriding of the SVC typically observed in the superior caval ASD but not for the high prevalence of PAPVC associated with it. An elegant echocardiographic study on SVDs from Children's Hospital Boston has shown that the deficiency in the wall that normally separates the right pulmonary veins or SVC and the RA is the leading cause of this particular defect.[17] Depending on the structures involved in this anomalous process, different subsets of ASDs (with one or more right pulmonary veins overriding the septum secundum) will occur.

Finally, a CoS defect may be due to a deficiency in the remnant of the left horn of the SV, which extends along the entire length of the CoS to reach its orifice. This defect is generally found in association with persistence of a left SVC.

Advances in genetic analysis and molecular biology have striven to investigate the embryonic mechanisms of cardiac looping, chamber development, myocardial cell growth, and cardiac valve formation. At present, the origin of most of the complex genetic traits of congenital heart disease remains to be completely defined. Studies focused on chromosomal abnormalities, autosomal dominant syndromes, and genetic linkage analysis of relatives of patients presenting with minor degrees of congenital heart disease have led to the detection of only a handful of the genes responsible for the development of congenital heart malformations.

Specifically (with regard to atrial septation defects), it is known that the Holt-Oram syndrome (association of ventricular septal defect and ASD with limb abnormalities) is the product of mutation of gene TBX5 in locus 12q24. Several investigations have revealed a heterozygous mutation in gene NKX2.5 in locus 5q34 in families with ASDs and conduction abnormalities.[14]

## ANATOMIC CONSIDERATIONS

The five more commonly occurring variants[18] of defects of the interatrial septum are (1) OS defect and PFO, (2) OP defect, (3) CoS defect, (4) SV ASD and its association in the superior position with PAPVC, and (5) SS.

The OS defect is the most common of all types of interatrial communications (80 percent). This defect is confined within the borders of the fossa ovalis (Fig. 64-3) and its name is in fact almost a misnomer, since the OS defect is actually the final result of deficiency in the development of the septum primum. OS defects may differ in size and morphology, depending on the degree of reabsorption of the septum primum and on the deficiency of the flap valve of the fossa ovalis. The degree of its absence varies from partial deficiency to complete absence, when the inferior border of the septum primum becomes continuous with the posterior wall of the IVC. Surgeons must bear this anatomic peculiarity in mind in order to distinguish the inferior edge of the defect from the eustachian valve: misperception of this may result in inadvertent baffling of the IVC to the LA. A PFO is found in approximately 30 percent of normal hearts. In the absence of left-to-right shunt (and with LA pressure > RA pressure), the lack of closure of the natural flap valve may be considered not a true interatrial communication. Intermittent shunting across the PFO may occur spontaneously or during provoking maneuvers that increase RA pressure, such as coughing or the Valsalva maneuver.

Because of the direct continuity between the leftward aspect of the IVC wall and the septum primum, when the floor of the fossa ovalis is absent and an ASD extends toward the IVC, the inferior caval ostium overrides the defect onto the LA. This anatomic pattern (or inferior SV ASD) may occasionally promote right-to-left shunt with cyanosis. Moreover, the proximity of right pulmonary veins to the deficient posteroinferior rim of the ASD favors a functional hemianomalous pulmonary venous connection.

At the extreme of septal maldevelopment is the common atrium, which may be described as an association of several defects involving structures of different embryonic origin. The association of a complete lack of the septum primum and of the superior and inferior limbi has been classified by some authors as the common atrium. This lesion is generally found in atrial isomerism in association with a persistent left SVC draining into an unroofed CoS.

Defects located beneath the inferior limb of the primary septum (10 percent of all ASDs) are associated with morphologic abnormalities of the atrioventricular valves and are described in Chapter 66. Even if these are to be invariably classified as AVSD or endocardial cushion defects, the OP defect has been reported in hearts with no evidence of AVSD morphology.[19]

The CoS defect (Fig. 64-4) results from variable fenestrations along the common wall between the CoS and the posterior aspect of the LA. It represents an infrequent type of ASD, accounting for only 1 to 2 percent of all defects of the interatrial septum. The ostium of the CoS is invariably present in its expected position along the posteroinferior margin of the triangle of Koch (see Chapter 59). This defect is generally found in association with a number of lesions, most frequently with persistence of the left SVC: these associated lesions (with the extreme form being the total absence of the CoS wall) determine the spectrum of the "unroofed coronary sinus syndrome." A surgical classification has been proposed that categorizes CoS defects into proximal, medial, and distal according to the site of the deficiency of the CoS wall along its length.[20–22]

The superior SVD (SV ASD) is associated with PAPVC in 5 to 10 percent of cases. This malformation (also known as superior caval ASD) is located in the posterosuperior

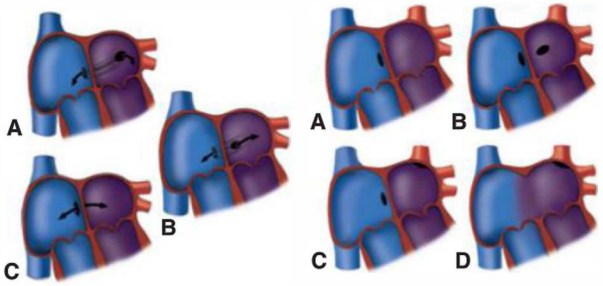



**FIGURE 64-4** Coronary sinus (CoS) defect with and without left superior vena cava (LSVC). Left panel: Proximal (**A**) and midportion unroofing (**B**) of the coronary sinus, resulting in interatrial communication. (**C**) Complete absence of the roof. Right panel: (**A**) Persistent LSVC with intact CoS roof. The roof of CoS draining the LSVC can be fenestrated (**B**) or absent (**C**) and can be associated with absence of the interatrial septum (**D**). (From deLeval M. Anomalies of the systemic venous return. In: Stark J, deLeval M (eds). *Surgery for Congenital Heart Defects*, 2nd ed. Philadelphia: Saunders, 1994:320,323. With permission.)

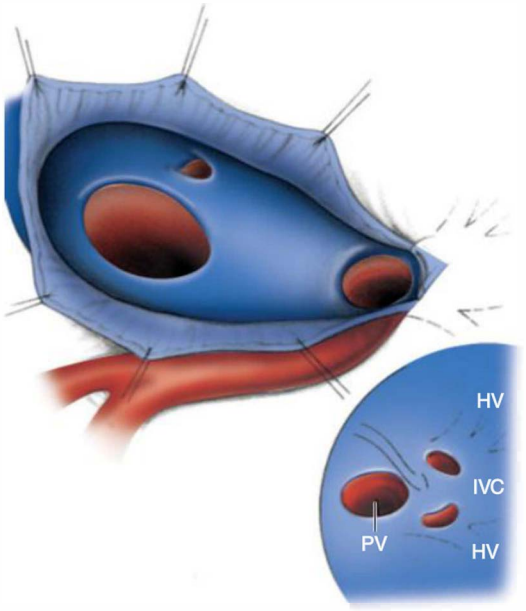



**FIGURE 64-6** Schematic representation of scimitar syndrome as seen through the right atrium. In the figure, a large fossa ovalis ASD is also represented. The anomalous draining vein enters the IVC right above the hepatic veins (inset). IVC, inferior vena cava; HV, hepatic vein; PV, pulmonary vein. (From Stark J. Secundum atrial septal defect and partial anomalous pulmonary venous return. In: deLeval M, Stark J (eds). *Surgery for Congenital Heart Defects*, 2nd ed. Philadelphia: Saunders, 1994:350. With permission.)

atrial septum, cranial to the superior limbic band. The most common position for the site of drainage of the anomalous pulmonary veins is at the superior atriocaval junction (Fig. 64-5). In 95 percent of cases with PAPVC, two right pulmonary veins (upper and middle lobes) are involved, but there may be three or even four pulmonary veins connected to the proximal SVC or SVC–right atrial junction. The SVC typically overrides the atrial septum and may result in right-to-left shunting across the ASD. When this defect is associated with the lack of the posterior limbus (posterior ASD), pulmonary venous drainage is somewhat anatomically unclear, although it flows functionally into the RA. When anomalous drainage of the right pulmonary veins is found with an intact posterior limbus or OS ASD, the anatomy is clear and a true PAPVC is present.

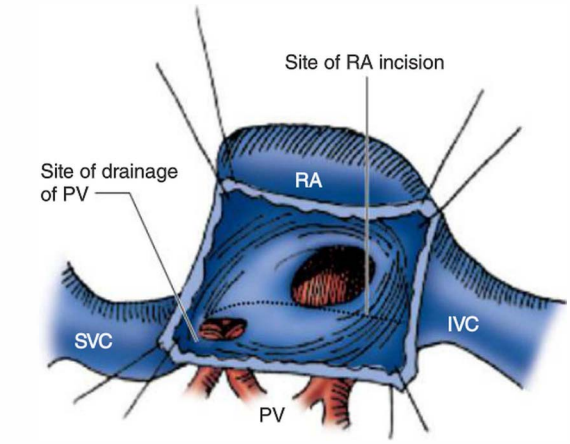



**FIGURE 64-5** Superior sinus venosus ASD, as seen through a right atriotomy. SVC, superior vena cava; IVC, inferior vena cava; RA, right atrium; PV, pulmonary vein. (From Jonas RA. *Comprehensive Surgical Management of Congenital Heart Disease.* London: Arnold, 2004:228. With permission.)

In SS (Fig. 64-6), an anomalous right pulmonary venous trunk (generally draining the entirety of the right lung) descends in a craniocaudal direction to connect to the IVC, generally above the IVC–RA junction.[23] This anomalous trunk usually descends along the right border of the pericardium. It has a crescent-like morphology (scimitar shape) and, at the level of the right hemidiaphragm, passes transversely and anteriorly to the hilum of the right lung to connect to the IVC. The radiologic appearance of this pathology is characteristic (Fig. 64-7). The interatrial septum may be intact or an OS/PFO defect may be associated to SS. SS generally occurs in association with several extracardiac malformations, such as right lung hypoplasia (invariably associated with a marked right mediastinal shift with dextrocardia), right pulmonary artery (PA) stenosis and/or hypoplasia and right lower lobe (RLL), or bronchopulmonary sequestration. Diaphragmatic anomalies occur in approximately 20 percent of cases, and consist of right lung herniation through the foramen of Bochdalek or of abnormal attachment of the hemidiaphragm. Very occasionally, a CPV trunk drains the entire right lung and descends in a craniocaudal direction to

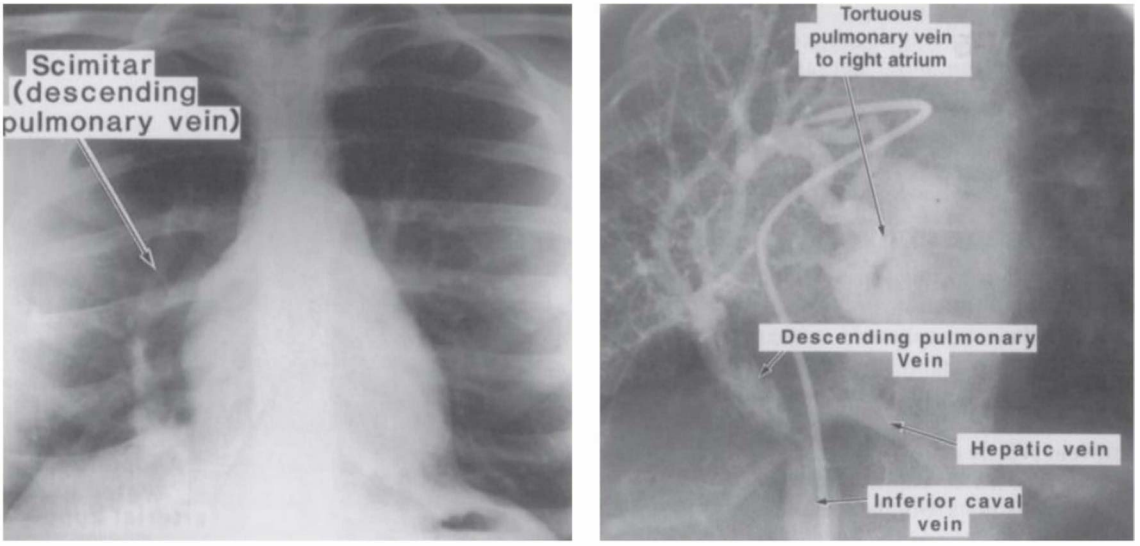



**FIGURE 64-7** Characteristic radiologic appearance of scimitar syndrome. On Chest x-ray, a right-lower-lung-field crescentic vascular marking is visible (left). Cardiac catheterization discloses the anomalous right inferior pulmonary vein draining into the inferior vena cava (right). Tortuous anomalous venous return from the upper and middle lobes to the right atrium is also seen. (From Anderson RH, Baker EJ, Mccartney FJ, Rigby ML (eds). *Paediatric Cardiology,* 2nd ed. Philadelphia: Churchill Livingstone, 2000. With permission.)

connect with the posterior LA. This peculiar arrangement shares similar radiologic findings with SS but has no clinical significance.

## PATHOPHYSIOLOGY

The magnitude of left-to-right shunting is determined by the size of the communication and relative compliance of the ventricles. As for ventricular septal defects (VSDs), the location of the ASD has very limited influence on the magnitude of the pulmonary-to-systemic flow ratio ($Q_p$:$Q_s$).

If even a relatively small subtricuspidal shunt (because of the high-pressure gradient between the ventricles) can give rise to a large left-to-right shunt, only a large ASD leads on the contrary to a large shunt. In the presence of a large ASD with an area similar to that of the mitral valve (MV), pulmonary venous return will be equally distributed between the ASD and the MV. If the ASD is restrictive, blood flow will be diverted preferentially toward the MV, and the $Q_p$:$Q_s$ will rarely exceed 2:1.[18]

Only in cases of associated acquired and/or congenital heart defects that increase LA pressure (as in systemic hypertension, MV stenosis, coarctation of the aorta, patent ductus arteriosus and VSD) will flow across the atrial septum be increased independently of ASD area. If a large defect is present atrial pressures will equalize. In this circumstance, the respective flows across mitral and tricuspid valves will vary according to the relative compliance of the ventricles. In the early months of life, the thickness of the right ventricle (RV) exceeds the thickness of the left (LV), resulting in right-to-left shunting. After the neonatal period, the LV exceeds in thickness the RV, yielding a net left-to-right shunt. The effect of atrial-level shunting results in enlargement of the RA, RV, and PAs. The overload is usually well tolerated by the RV, and heart failure seldom develops in childhood. Occasionally, heart failure occurs in infancy, but it is very rare and is generally related to various extracardiac conditions. In cases of ASD with pulmonary hypertension (PHT—as in rare pediatric cases and in some adult patients) RV thickness will increase and compliance of the RV may be similar and/or higher than that of the LV. In these cases, a right-to-left shunt will appear with a marked degree of cyanosis and hypoxia, with clinically evident heart failure.

The increase in pulmonary blood flow, over several years, may promote the development of PHT in adulthood. The onset of PHT is variable and, at present, it is not possible to reliably predict which patient will develop PHT and at what age. This variability may depend on the multiple factors involved in the pathogenesis of PHT: recurrent pulmonary infections with microatelectasis, progressive increase in left-to-right shunt with enlargement of the ASD, individual endothelial vascular hyperreactivity, thrombotic and thromboembolic lesions of pulmonary arteries, failure of the pulmonary vascular resistance to drop, and association with acquired heart diseases that would promote LV dysfunction (such as MV prolapse, coronary artery disease, and systemic hypertension among others).[24]

In the presence of an interatrial communication, a potential reverse shunt at atrial level may account for paradoxical embolization in the cerebral circulation. This condition may depend on instantaneous trans-ASD gradient modifications,

as well as the size, morphology, and position of the defect along the atrial septum. A large meta-analysis has indicated the presence of interatrial septal abnormalities as significantly associated to paradoxical embolism.[25] Furthermore, the incidence of PFO among adults suffering from cerebrovascular accidents was found to be higher than in the unaffected population. Coagulation disorders or thrombocytosis may also play a role in the pathogenesis of paradoxical embolization.

## CLINICAL FEATURES

The reported incidence of isolated ASD ranges from 7 to 14 percent, with a slight female predominance. This fairly broad range is due to the inclusion criteria used in the reports over the past few decades that considered ASDs and PFOs referred to surgery as identical pathologic entities. In the setting of other congenital heart defects, their incidence ranges from 33 to 50 percent.[26] The wide use of echocardiography has led to the detection of ASDs of any size and at any age. Several investigators have reported the results from populations of children bearing an ASD at long-term follow-up.[27,28]

The conclusions emerging from these studies may be summarized as follows:

- ASDs less than 6 mm in diameter, detected in infancy, almost always restrict spontaneously.
- ASDs between 6 and 8 mm in diameter, classified as hemodynamically insignificant, may restrict even after 5 years of age and not necessarily below 18 months of age, as once thought.
- ASDs greater than 8 mm in diameter may increase in size during childhood, although a restrictive physiology is still a more common possibility.

Among all diagnosed ASDs, the reported incidence of SVDs varies between 2 and 10 percent.[29] This relatively high incidence may be due to diagnostic bias, the incidence of SVD being higher in studies focusing on cohorts with more "complex" ASDs.

The signs and symptoms of ASD and PAPVC are strictly related to the direction and magnitude of the shunt and with the age of the patient at detection. $Q_p:Q_s$ is greater than 1 in predominant left-to-right shunt. When $Q_p:Q_s$ is below 1.8:1,[30] clinical signs and symptoms are typically mild or absent in both pediatric and adult patients. When $Q_p:Q_s$ exceeds 2:1, signs and symptoms often become clinically evident. In this subset of patients the classic "fixed split second heart sound" and systolic pulmonary flow murmur are typically audible. Reduced exercise capacity and a history of recurrent respiratory infections may be present in childhood as well as in adolescence. Several other conditions must be taken into consideration in the differential diagnosis, such as innocent murmur associated with a normal cardiovascular state and pulmonary valve stenosis; this is usually audible in the higher upper left sternal border, presents with an early systolic ejection sound, and, in cases of stenosis of the PA branches, is transmitted toward the back. In these conditions, however, splitting of the second heart sound is absent.

In cases of PAPVC, the amount of shunt through the abnormally connected veins will often result in heart failure, pulmonary infections, growth retardation, and poor effort tolerance even in infancy.

In adult patients, an episode of paroxysmal atrial fibrillation may represent the first clinical event.

The development of PHT and poor exercise capacity with cyanosis, dyspnea, and migraine often represents the pathophysiologic evolution of an ASD toward irreversible changes within the pulmonary vasculature (Eisenmenger syndrome).

Lastly, PFO with or without associated aneurysm of the atrial septum may promote paradoxical embolism and should be clinically ruled out in the context of an acute cerebrovascular event.[30,31]

SS is a rare cardiac malformation diagnosed in approximately 2 of 100,000 live-births and that is often associated with other congenital heart lesions, variable hypoplasia of the right lung, and PHT.[32] As mentioned in the morphologic considerations, the constant feature is a single trunk draining venous return from the entire right lung into the IVC. There are often accessory systemic-to-pulmonary collaterals from the abdominal aorta to the RLL. When symptoms emerge during infancy, other anomalies (such as septation defects or left ventricular outflow tract obstruction) are often associated. The presence of aortopulmonary collaterals does not generally have a critical impact on the development of heart failure, since the hypoplastic lung is typically underperfused. Furthermore, pulmonary sequestration of the right lung (in the absence of hypoplasia) usually involves a maximum of two pulmonary segments. When SS is discovered in late childhood or in adulthood, the patient may be asymptomatic or, more often, be a history of recurrent respiratory tract infections, cough, and dyspnea. Heart failure, if present, is of mild degree. Intracardiac lesions are generally absent, and extralobar sequestration of a RLL is observed in approximately 50 percent of cases. $Q_p:Q_s$ usually ranges from 1.5 to 3.1.[32]

As mentioned above, physical examination in early childhood is often less than revealing unless the shunt is substantial or there are associated lesions.[33] In large ASDs, a left parasternal lift can be detected, while a fixed, split second heart sound is typically audible, together with a soft "crescendo–decrescendo" systolic flow murmur over the pulmonary valve's auscultation focus. The second heart sound can be prominent in case of PHT. Clinical evidence of overcirculation is rare, as is cyanosis in cases without severe PHT. Cyanosis with streaming can be observed in superior or inferior defects where the SVC or IVC "straddles" the interatrial septum at the site of the defect, resulting in a functional right-to-left shunt of variable magnitude. This is, from a clinical standpoint, often underdetected. In a recent review of infants and children with ASDs without associated lesions treated at our institution, only 2 of 278 patients was cyanotic on presentation.

Even though symptoms might not present until the fifth decade of life, approximately 50 percent of adults will

manifest exertional dyspnea by the age of 20; among adults with sizable defects, almost all will be symptomatic by the sixth decade of life.[23] If untreated, adults with large ASDs show a 75 percent mortality rate within the fifth decade, rising to nearly 90 percent in the sixth decade of life.[34]

Symptomatic supraventricular arrhythmias often complicate the natural history of ASDs diagnosed in adulthood, the most common among them being atrial fibrillation followed by atrial flutter. In the elderly, sick sinus syndrome might be the initial rhythm abnormality upon presentation; given the risk of paradoxical embolization, insertion of a transvenous pacing system without percutaneous or surgical ASD closure is contraindicated.

Paradoxical embolization should be strongly suspected as the pathophysiologic entity underlying cryptogenic strokes, although the very low prevalence of venous thrombosis and procoagulant conditions make this a rare entity in infants and children. The presence of an atrial septal aneurysm (in the absence of interatrial communication) was considered a predisposing factor for paradoxical embolism; data from the SPARC study[35] and the Patent Foramen Ovale and Atrial Septal Aneurysm Study Group[36] did not find this morphologic variant of septal morphology to be an independent risk factor for embolism in the absence of a PFO or an ASD.

## DIAGNOSTIC STUDIES

In children, electrocardiographic examination almost always discloses normal sinus rhythm and incomplete right bundle branch block, with a right axis deviation on the frontal plane between 90 and 120 degrees. In adulthood, atrial flutter and fibrillation are more frequent after the fourth decade of life, and increase in incidence with advanced age. In this subset of patients, the counterclockwise loop on the frontal plane shows less rightward shift and complete right bundle branch block, with a prominent R' wave (>15 mm) on the right precordial leads in almost 50 percent of patients with PHT.

Radiologic findings are dependent on the magnitude of $Q_p$:$Q_s$, with plethoric lung fields typically seen in the presence of larger defects. Cardiomegaly also reflects the amount of blood flow across the ASD, with heart diameter increasing with a higher degree of left-to-right shunt, usually associated with a prominent radiologic projection of the PA trunk. Once obstructive pulmonary vascular changes and structural PHT worsen (leading to Eisenmenger syndrome and right-to-left shunting) cardiac size decreases, the central PAs become prominent and their branches appear truncated, with oligoemic peripheral lung fields (Fig. 64-8).

SV ASDs may be associated with additional pathognomonic findings, such as a significant prominence of the upper right vascular pedicle, in cases of superior caval ASD with right PAPVC or the right inferior crescentic shadow of the anomalous pulmonary vein on the frontal plane in SS.

Transthoracic echocardiography (TTE) is the diagnostic modality of choice for ASD. M-mode echocardiography provides indirect evidence of ASD, revealing right ventricular (RV) overload with increased RV diameter and, in most cases, flattened or paradoxical ventricular septal motion. Even though these ultrasonographic findings clearly support the evidence of increased right chamber preload, they are not specific; similar findings are in fact observed with several

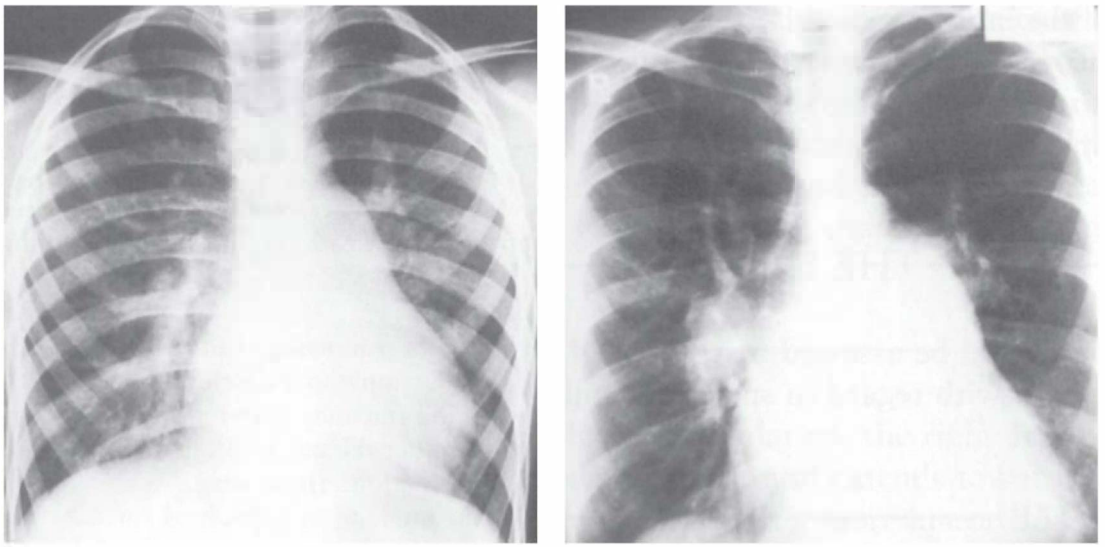


**FIGURE 64-8** Radiologic findings in atrial septal defect. Left: Pulmonary overcirculation with increased interstitial vascular markings and cardiomegaly. Right: Patient with advanced pulmonary vascular obstructive disease in the setting of an untreated atrial septal defect. Cardiomegaly, prominent central pulmonary arteries, and oligoemic peripheral lung fields. (From Anderson RH, Baker EJ, Mccartney FJ, Rigby ML (eds). *Paediatric Cardiology,* 2nd ed. Philadelphia: Churchill Livingstone, 2000. With permission.)

other cardiac diseases, such as, for example, tricuspid and pulmonary regurgitation and total or PAPVC, among others. Two-dimensional echocardiography is much more specific for the diagnosis of an ASD. The reported detection rate ranges from 89 to 99 percent for OS defects[37] with the use of subcostal and modified longitudinal scans (Fig. 64-9). Color Doppler-flow mapping techniques can be performed to confirm the presence of an ASD and to visualize the direction of the shunt, with good correlation with findings at cardiac catheterization.[38]

CoS ASDs may be suspected in patients with echocardiographic evidence of a dilated CoS. Besides the common findings of dilated RV, more posterior scanning views (subcostal and apical four chamber) can directly reveal the communication between the CoS and LA.

Contrast echocardiographic evaluation may better reveal the suspected ASD. In cases of unidirectional left-to-right shunt, the observation of a negative washout into the RA may confirm the suspicion of a shunt at the atrial level, whereas in cases of right-to-left shunting, the detection of contrast bubbles of agitated saline in the LA provides direct evidence of an inverted shunt.

TTE is much less reliable in patients with uncommon defects at the atrial level, such as SV ASDs and PAPVCs, with a sensitivity of approximately 70 percent.[39] Because of the shorter distance between probe and defect, transesophageal echocardiography (TEE) overcomes inadequate visualization, especially in older children and adults, in whom diagnostic sensitivity and specificity for SV ASDs and PAPVC approach 100 percent.[40] Longitudinal scans are particularly useful in the delineation of the upper atrial septum, while short-axis views may be fundamental for assessment of the pulmonary–systemic venous connection.

Three-dimensional TEE currently represents the most sophisticated tool for the morphologic evaluation of ASDs that are potential candidates for percutaneous closure (Fig. 64-10). Three-dimensional reconstruction allows for precise localization of the defect. Delineation of its proximity to valvular structures, visualization of the venous ostia and adequacy of margins, as well as provision of an immediate assessment of defect's obliteration following device deployment.[41] Similar advantages have been reported with the recent introduction of intravascular ultrasound (IVUS) techniques for diagnosis and treatment of ASDs.[42,43]

Although the vast majority of ASDs are diagnosed accurately with conventional ultrasonography, imaging techniques [magnetic resonance imaging (MRI) and computed tomography (CT)] have gained wide acceptance in defining anomalous venous connections in patients with complex ASDs.[44]

Cardiac catheterization is not indicated in the preoperative diagnostic workup of ASDs in children, adolescents, and young adults. Given the reliability of TTE and TEE, cardiac catheterization is currently only indicated in those cases with inadequate imaging or for complete assessment of complicated ASDs. Such conditions may include severe heart failure in infants, cases of suspected PAPVC not clearly defined by ultrasound, SS, and, in the adult population, associated

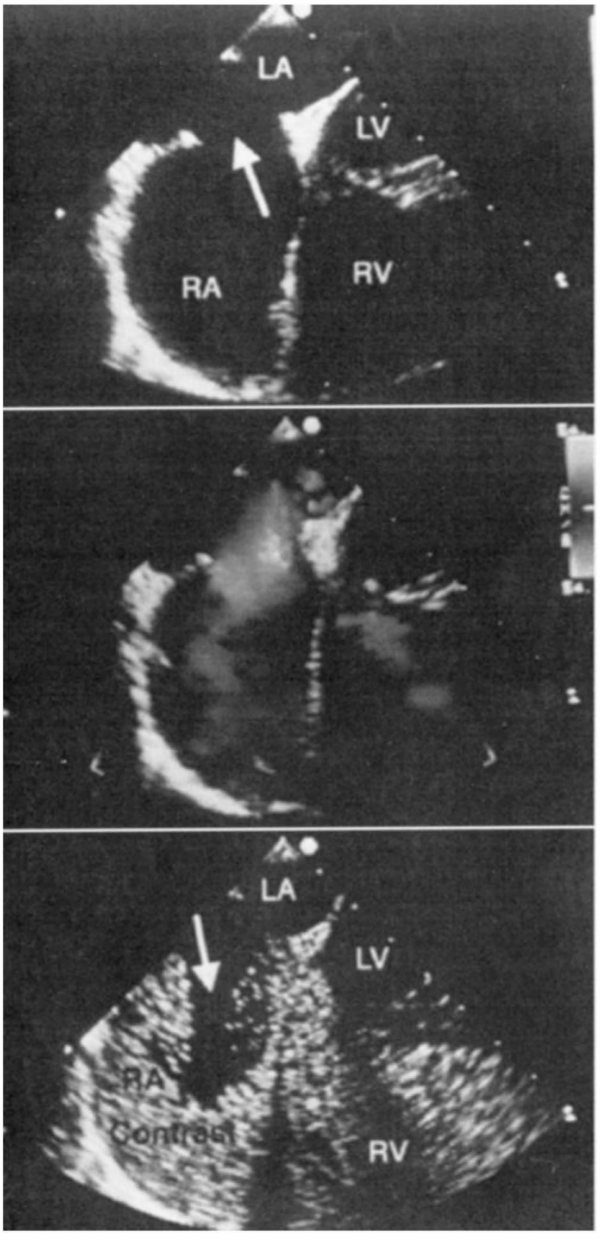



**FIGURE 64-9** Transesophageal echocardiography in a patient with a large secundum-type ASD. A large defect (arrow, top panel) is visible between the right and left atria. Color-flow Doppler interrogation reveals unrestricted left-to-right shunting (middle). Systemic venous injection of agitated saline reveals a "negative washout" of saline bubbles secondary to the left-to-right shunt, with paucity of contrast seen in the left atrium (lower panel). (From Kouchoukos NT, Blackstone EH, Doty DB, et al. (eds). Atrial septal defect and partial anomalous pulmonary venous connection. *Kirklin/Barratt-Boyes Cardiac Surgery,* 3rd ed. Philadelphia: Churchill-Livingstone, 2003:726. With permission.)

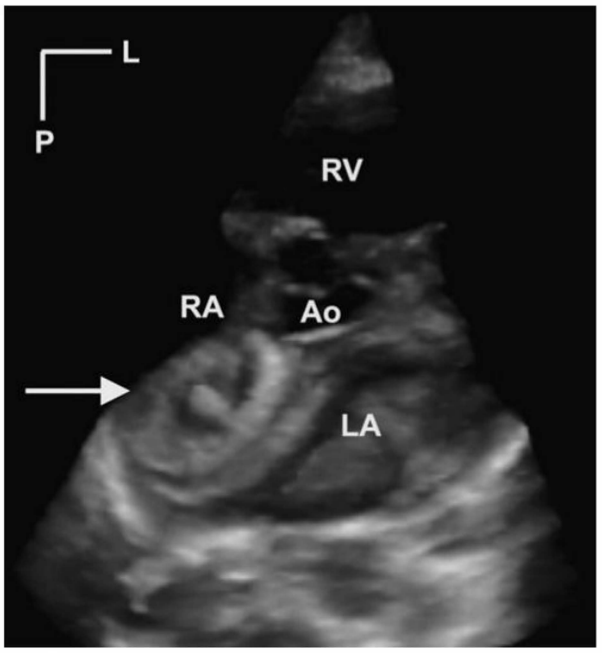



**FIGURE 64-10** Three-dimensional transesophageal echocardiogram following deployment of an Amplatzer Septal Occluder device (arrow). Ao, Aorta; LA, Left atrium; RA, Right atrium; RV, Right ventricle. (Courtesy of Dr. William Ravekes, Division of Pediatric Cardiology, Johns Hopkins Hospital.)

acquired heart lesions (such as valvular pathology and/or coronary obstructive disease).

A full invasive diagnostic study with hemodynamic evaluation is indicated in patients with secondary PHT and an ASD. Feasibility of surgery is judged upon calculation of pulmonary vascular resistance and its eventual decrease according to the administration of oxygen, inhaled nitric oxide (iNO), and infusion of prostacyclin analogues. With a significant decrease in pulmonary arterial pressure and resistance, the patient should be considered a surgical candidate. Lack of response to the abovementioned pulmonary vasodilators contraindicates surgical intervention. In intermediate cases, fenestrated ASD closure can be considered.

## NONOPERATIVE MANAGEMENT

As already mentioned, indications for surgical intervention are rarely met in children younger than 2 years of age. Failure to thrive and need for medical therapy or correction is, however, more frequent in infants and children with a common atrium or chromosomal abnormalities.[44,45] There are also other conditions in which early crossover from medical to surgical management might be indicated, such as otherwise unexplained PHT in infancy[46] and concomitant association of an enlarged CoS (atypical left cor triatriatum), functionally similar to totally anomalous pulmonary venous connection (Fig. 64-11).[47] If the child presents symptoms and/or evidence of RA/RV enlargement at echocardiography, continuing medical management until 5 years of age could be justified. Several investigators have in fact reported spontaneous restriction, even in those cases with heart failure in infancy.[28] In the interim (even though rarely needed), diuretics and angiotensin antagonists can be used to control symptoms and progression of heart failure, while cardiac status is monitored echocardiographically on a yearly basis. In cases not amenable to a conservative approach and not showing a tendency toward restriction, intervention can usually be postponed until 1 to 2 years of age, at a time when morbidity and mortality from ASD closure are usually negligible.[48]

The advantage of surgical intervention in ASD and/or PAPVC in adult and elderly patients has been debated.[49] The Canadian consensus conference on adult congenital heart disease[50] clearly underscored that any "significant ASD warrants intervention," implying that any ASD with RV volume overload, atrial arrhythmias, and/or late heart failure should be treated, given the low risk of surgical and percutaneous intervention.

Closure of the defect is not recommended in patients presenting with advanced pulmonary vascular obstructive disease. Medical treatment is indicated and should be individually tailored according to symptoms, comorbidities, and cardiovascular complications.

## SURGICAL TREATMENT

Closure of ASDs is conventionally performed through a median sternotomy, although a variety of alternative approaches are also utilized.

We will outline the surgical approach to closure of ASDs, along with a brief description of specific considerations that apply to more complex variants of ASD, namely CoS, SV ASD/PAPVC, and SS. A description of the techniques utilized for more complex subtypes of anomalous systemic venous connections and atrial septation is beyond the scope of this chapter.[51,52]

A median sternotomy is performed and bypass instituted with bicaval drainage and moderate hypothermia (30°C–32°C); the repair accomplished with either fibrillatory or cardioplegic arrest. Following cardiac arrest, caval snares are tightened and an oblique atriotomy is performed. Depending on preoperative localization of the defect, cephalad or caudad extension of the atriotomy is carried out. The LA is usually vented directly across the defect and the anatomy carefully evaluated, including the morphology of the mitral and tricuspid valves. The RV outflow tract is also assessed, and all pulmonary and systemic venous ostia are accounted for.

The technique chosen (primary or patch closure) to repair the defect is determined by the size, location, and shape of the ASD. In our opinion, the majority of ASDs (within the

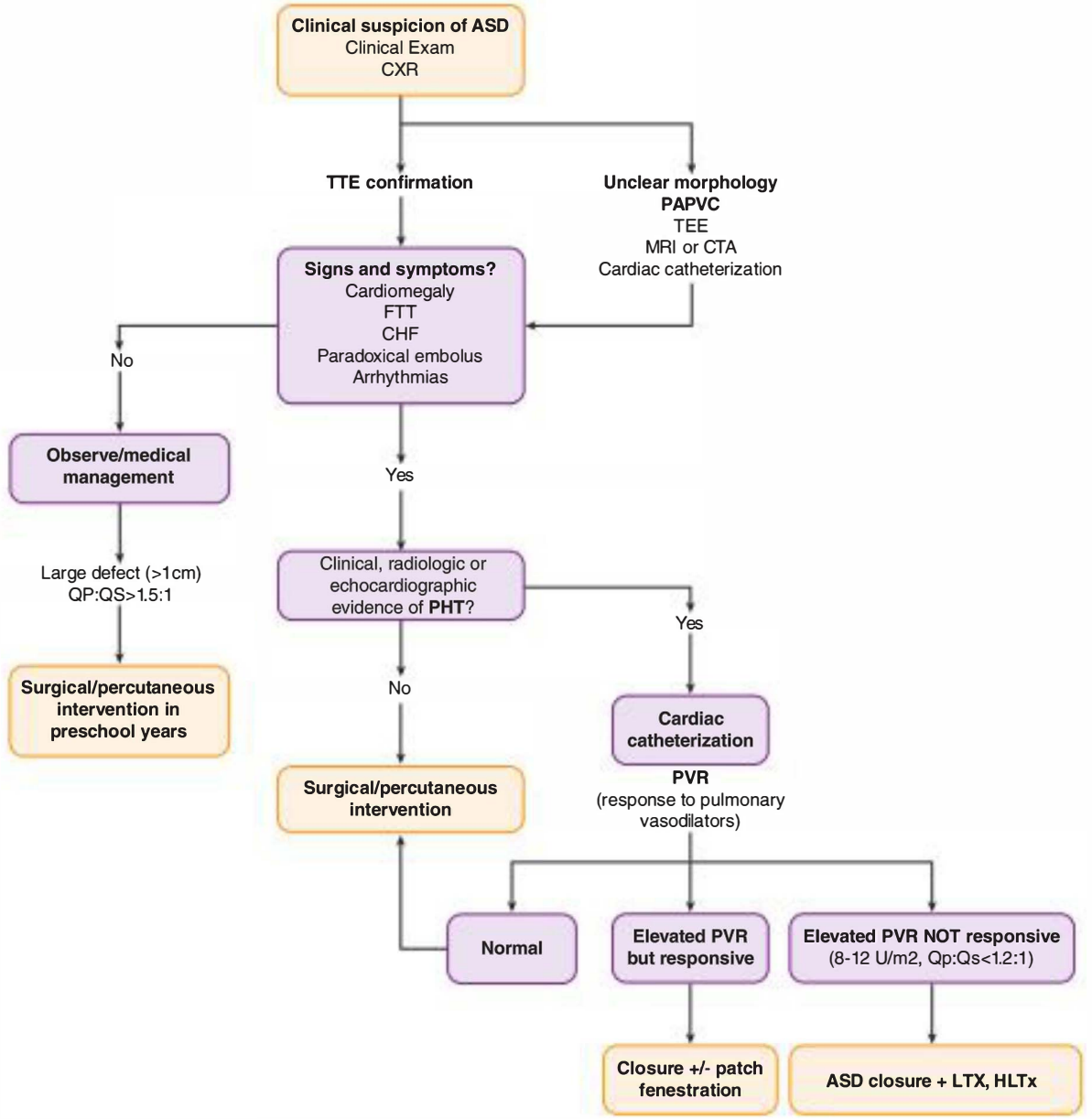



**FIGURE 64-11** Clinical decision-making algorithm for management of isolated atrial septal defects and partial anomalous venous connection. ASD, atrial septal defect; CHF, congestive heart failure; CTA, CT a ngiography; CXR, chest x-ray; FTT, failure to thrive; HLTx, heart–lung transplantation; LTX, lung transplantation; MRI, magnetic resonance imaging; PAPVC, partial anomalous pulmonary venous connection; PHT, pulmonary hypertension; PVR, pulmonary vascular resistance; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

fossa ovalis, with the exception of the single atrium) can be closed with a continuous double-layer nonabsorbable suture (see Fig. 64-12), catching strong bits of the posterior and anterior limbic tissue of the atrial septum and starting from the caudal edge of the defect. It is obviously recommended that the right pulmonary veins not be restricted, the MV not distorted, and the nodes not injured. Patch closure can be easily performed with a portion of autologous pericardium, harvested at the beginning of the procedure and tanned in 0.6 percent glutaraldehyde (Fig. 64-13). Alternatively, polytetrafluoroethylene, bovine pericardium or Dacron patches can be utilized. The latter should, however, be avoided in the presence of known mitral regurgitation, as persistent regurgitant jets on the Dacron fabric have been associated with hemolysis. Given the known thrombogenicity of the aneurysmal fossa ovalis ASD, we routinely resect

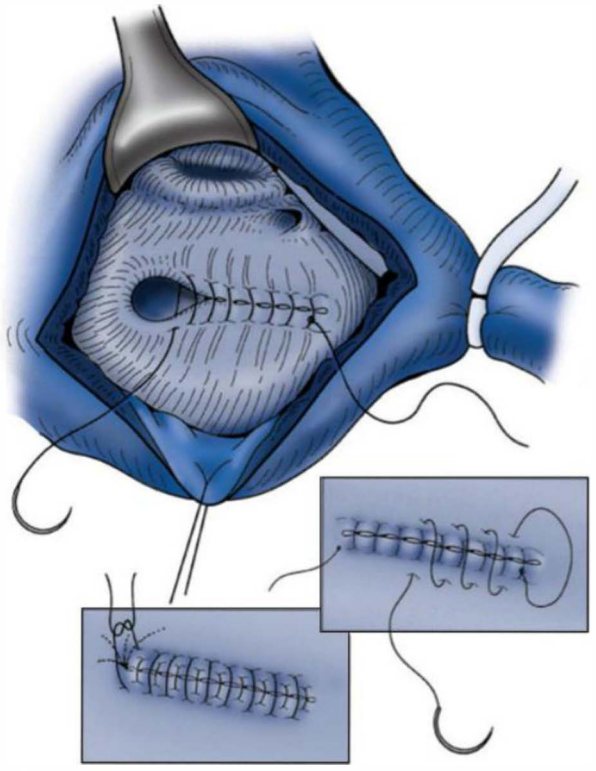


**FIGURE 64-12** Direct closure of ASD. A two-layer closure with nonreabsorbable suture is started at the inferior aspect of the oval-shaped defect and run in a cephalad direction (left side of the figure). (From Manning PB. Atrial septal defect. In: Gardner TJ, Spray TL (eds). *Operative Cardiac Surgery,* 5th ed. London: Arnold, 2004:595. With permission.)

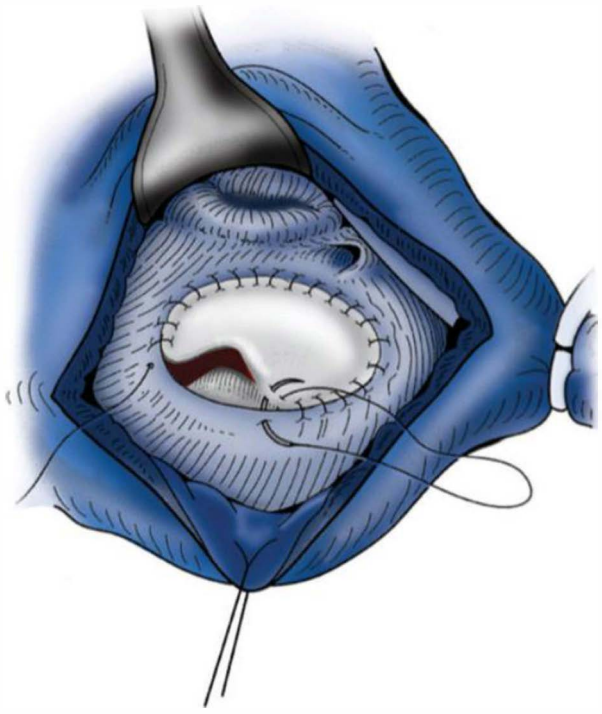


**FIGURE 64-13** Patch ASD closure. A patch of autologous pericardium is secured around the circumference of the defect with a running polypropylene suture. (From Manning PB. Atrial septal defect. In: Gardner TJ, Spray TL (eds). *Operative Cardiac Surgery,* 5th ed. London: Arnold 2004:596. With permission.)

the aneurysmal tissue and then perform patch closure rather than plicating or patching the redundant tissue.

In inferiorly located ASDs (Fig. 64-14), when there is deficiency of an inferoposterior rim, it is best to start patch closure in this area, proceeding from the IVC toward the more developed ASD rim. Modified ultrafiltration is carried out in our practice in all children with operative weight below 20 kg. Blood-conservation strategies (i.e., minimal priming of the circuit with autologous blood after cannulation and utilization of a "cell saver" system to scavenge and

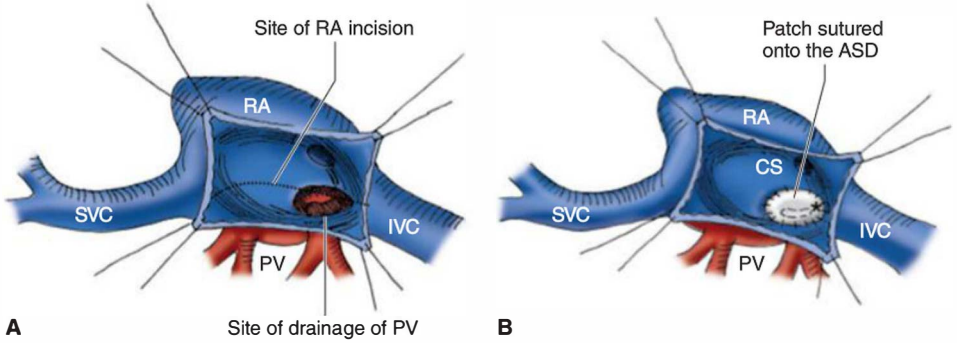



**FIGURE 64-14** **A.** Inferiorly located ASD, as seen through a RA (surgeon's perspective). **B.** Patch closure on inferiorly located ASD, as seen through a RA (surgeon's perspective). SVC, superior vena cava; IVC, inferior vena cava; CS, coronary sinus; RA, right atriotomy; PV, pulmonary veins; *, site of starting point of the suture line of the patch (see text). (From Jonas RA. *Comprehensive Surgical Management of Congenital Heart Disease*. London: Arnold, 2004:230. With permission.)

reinfuse shed blood) are considered for children with operative weight above 20 kg.

For closure of an isolated CoS defect, it is sufficient to simply close off the CoS bearing in mind that the cephalad margin is very close to the atrioventricular node. Since the tissue on that side is fairly soft, surgical closure with a patch secured with a continuous nonabsorbable suture is advisable. To avoid the atrioventricular node, the suture line should remain (anteriorly and superiorly) very deep within the CoS, taking small bites of tissue. Simple closure of the CoS will allow for a small obligatory right-to-left shunt from the unroofed CoS to the LA.

As mentioned in the morphology section, superior SV defects are located high in the septum secundum and are generally associated with anomalous connections of the right pulmonary veins in proximity of the superior cavoatrial junction. Direct cannulation of the SVC (as opposed to transatrial indirect cannulation) is optional and depends on SVC diameter and site of drainage of the anomalous pulmonary veins. A vertical incision (posterior to the sulcus terminalis and sinoatrial node and anterior to the pulmonary veins) is the standard approach. The right atriotomy is extended across the superior atriocaval junction, well above the superior margin of the anomalously connected pulmonary vein. The LA is usually vented via the ASD. The defect is closed with a patch of autologous pericardium, baffling the right-sided pulmonary veins toward the LA (Fig. 64-15). To prevent stenosis of the SVC, the atriotomy is closed with a generous patch of autologous pericardium or, when the SVC is large, by direct running closure.

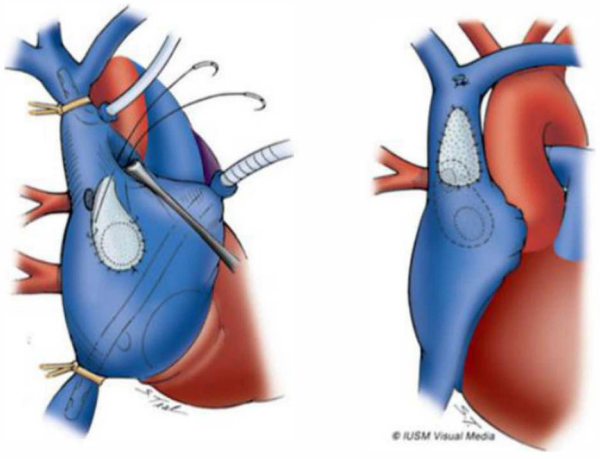



**FIGURE 64-15** Closure of superior sinus venosus atrial defect with partial anomalous pulmonary venous connection. Left: Through a superior right atriotomy, the defect is closed with a patch of autologous pericardium, rerouting the right superior pulmonary vein to the left atrium. Right: An additional pericardial patch is used to close the atriotomy extended across the superior atriocaval junction. (Copyright IUSM Visual Media.)

Since 2008, we have adopted a modified technique (Fig. 64-16A–E) for such type of defect. An "L-type" atriotomy (Fig. 64-16A) is the approach we have utilized with superior SV ASD undergoing correction at our institution. The upper edge of the right atriotomy is extended across the superior atriocaval junction, toward the superior margin of the anomalously connected pulmonary vein; the lower edge of the right atriotomy is extended toward the base of the right atrial appendage. The LA is usually vented via the ASD. The defect is closed with a flattened patch of autologous pericardium, baffling the right-sided pulmonary veins toward the LA. To prevent undue stenosis of the SVC, the atrium is closed with a "sliding plasty atrioraphy" that avoids the utilization of nonvascularized cavoatrial patch.

In those uncommon cases in which the SVC lumen appears to be extremely small or the anomalously connected veins drain very high above the RA-SVC junction, a more radical procedure should be considered (Warden procedure, Fig. 64-17). Through the right atriotomy, the anomalous return is rerouted to the LA. The atriocaval junction is transected and the distal aspect of the SVC is oversewn or closed with a patch so as to not compromise drainage from the anomalous pulmonary veins into the SVC. The proximal SVC is then anastomosed directly to the right atrial appendage. In older children, a polytetrafluoroethylene interposition graft can be used. In cases of PAPVC not associated with an ASD, the floor of the fossa ovalis can be excised, and the resulting unrestrictive communication utilized to baffle the anomalous return to the LA.

The surgical correction of SS is based on pre- and intraoperative localization of the anomalous pulmonary venous return. The anomaly is often amenable to rerouting toward the LA from within the IVC-RA junction (Fig. 64-18). If the anomalous pulmonary vein ostium is too low, the vein can be alternatively ligated at the diaphragm and either transected and anastomosed to the LA or RA or connected to the LA in a side-to-side fashion (Fig. 64-19). Variable depth of hypothermia is usually needed to aid in exposure.

## Alternative Surgical Approaches

After the introduction of alternatives to the relatively unattractive full sternotomy in the early 1980s, minimally invasive techniques for adult cardiac surgery gained great interest and popularity. The success of such alternatives led to enhanced public demand for a similar approach in the pediatric population, for whom constraints unique to the growing patient create a particular challenge. The simultaneous increasing popularity of percutaneous device closure further pushed heart surgeons to offer a reliable alternative to the standard, full sternotomy approach, while maintaining unaltered the almost negligible mortality and morbidity associated with a conventional sternotomy.

Among the minimally invasive approaches, mini-sternotomy, transxiphoid approach,[53] anterolateral thoracotomy,[54] posterolateral thoracotomy[55] and, most recently the

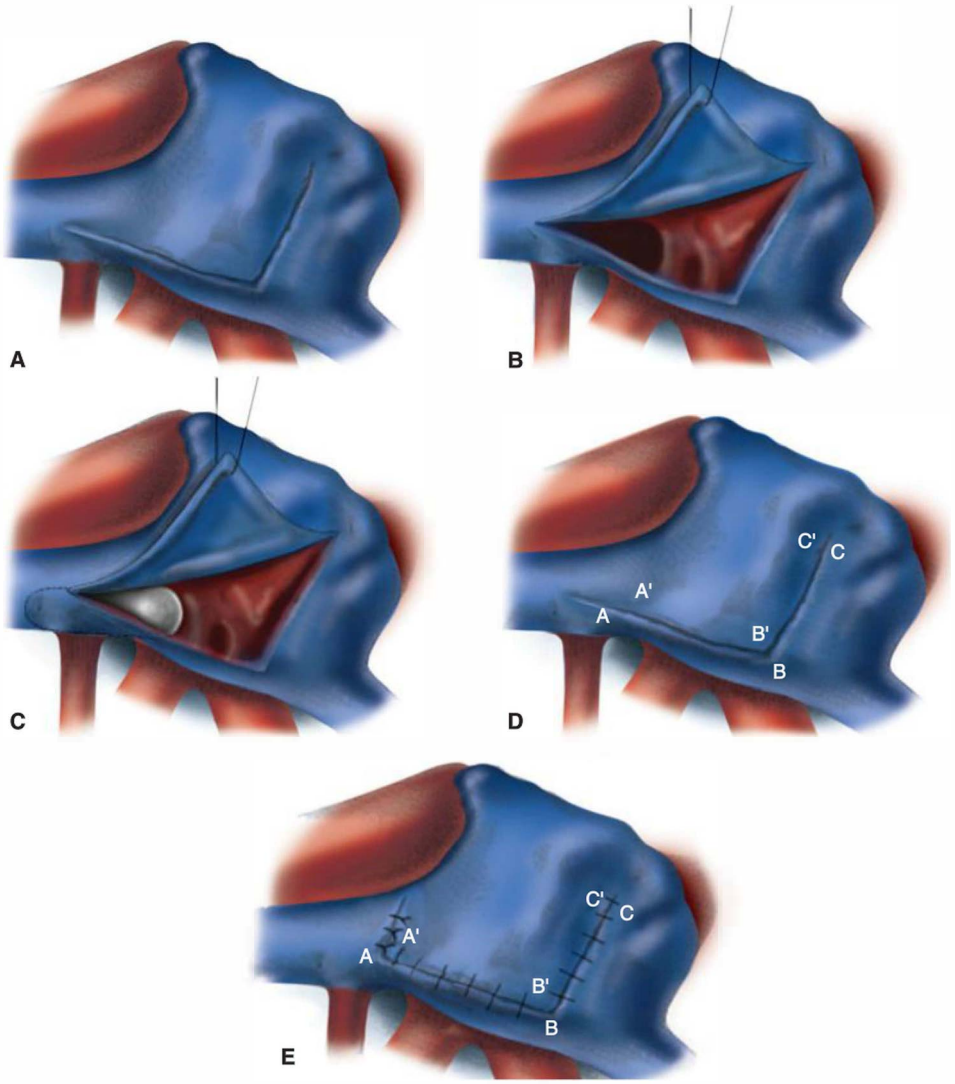



**FIGURE 64-16** Closure of modified superior sinus venosus atrial defect with partial anomalous pulmonary venous connection: after an " L-type" right atriotomy (**A**), a flap of atrium is lifted up (**B**) and the anatomy inspected; the defect is closed with a flattended patch of autologous pericardium, rerouting the right superior pulmonary vein to the left atrium (**C**). To close the atriotomy a "sliding plasty" is performed, in order to enlarge the pathway above the baffle with redundant atrial tissue (**D**, **E**).

midaxillary approach,[56] have gained in popularity. The analysis of all of these alternative options allows us to discover advantages and disadvantages for each of them.

Variations of the anterior approaches are represented by the longitudinal parasternal approach, introduced by Coosgrove and Sabik,[57,58], bilateral submammary incision, partial upper, partial lower sternotomy, and, finally the transxiphoidal incision.[59–63] The parasternal approach, consisting in the resection of one or more costochondral cartilages, allows a visualization of the cardiac and paracardiac structures comparable to the standard approach but with no need to violate chest wall integrity. Cannulation is performed directly through the operative field and the limited invasiveness has been demonstrated to lower postoperative pain and the length of hospitalization; unfortunately chest wall deformity in the growing patient and lung herniation have led several centers to abandon such approach. Because of the location of the defects, a lower sternotomy approach, has been adopted by most centers with success.[64] This form of access allows for optimal visualization of the structures and is preferable even when additional cardiac anomalies like patent ductus arteriosus, pulmonary valve stenosis and left SVC are associated with an ASD. The pliable infant thoracic cage also permits an exclusively subxiphoid incision, leaving the sternum intact.

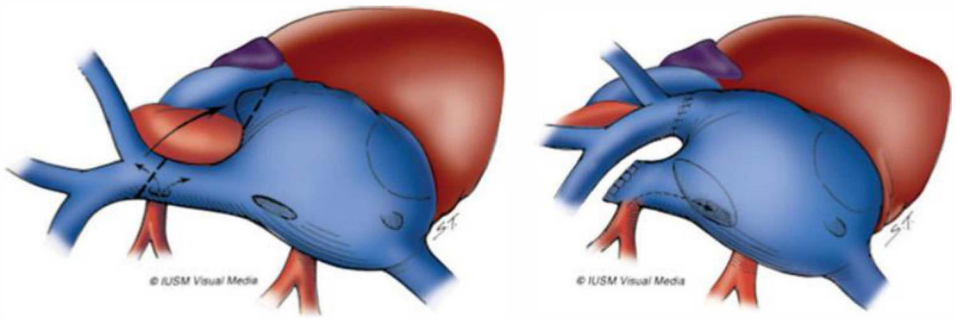



**FIGURE 64-17** Warden procedure. When the partial anomalous return to the superior vena cava is remote from the superior atriocaval junction, the superior vena cava (SVC) is transected (left). Pulmonary venous return is rerouted to the left atrium via an existing or surgically performed atrial septal defect, and the SVC is anastomosed to the right atrial appendage (right). (Copyright IUSM Visual Media.)

With lower sternotomy or hemi-sternotomy approaches, bicaval venous, aortic and cardioplegic cannulation are directly performed through the limited sternotomy incision, whereas this is not always achievable with an anterolateral or posterior thoracotomy approach. Furthermore, size and collapsibility of the great vessels in children are not condusive of peripheral cannulation.[65] The heart is either arrested with cardioplegia or induced ventricular fibrillation is utilized when aortic cross-clamping is difficult (thoracotomy). De-airing of the heart might also be more problematic with a thoracotomy approach. Several studies have demonstrated that recovery from a full-length sternotomy does not differ from the mini-sternotomy[66] in terms of pain tolerance, length of hospital stay and respiratory complications, an improved cosmetic result being the only advantage of the minimally invasive anterior approach. Likewise, the benefit derived from an anterolateral thoracotomy might be purely cosmetic.[67]

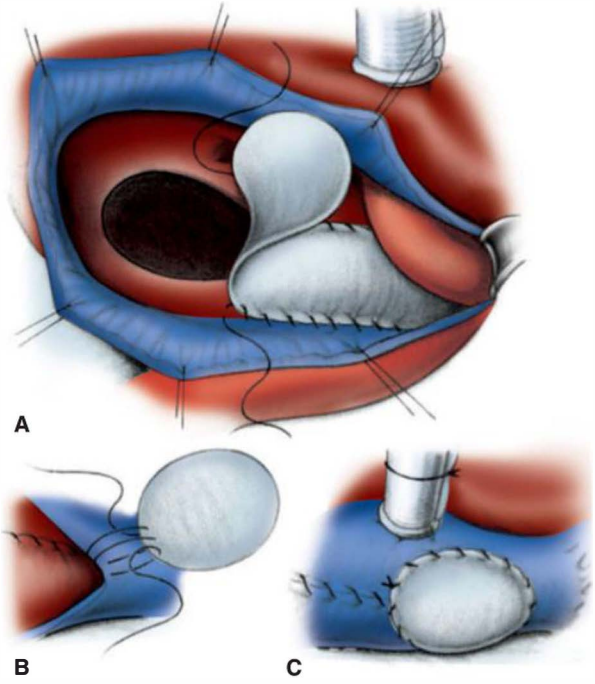



**FIGURE 64-18** Surgical correction of scimitar syndrome. An intracardiac baffle of autologous pericardium (**A**) is used to reroute pulmonary venous return to the left atrium via an ASD. The lower portion of the atriotomy is enlarged with a second patch to avoid stenosis of the inferior vena cava (**B**, **C**). (From Stark J. Secundum atrial septal defect and partial anomalous pulmonary venous return. In: deLeval M, Stark J (eds). *Surgery for Congenital Heart Defects*, 2nd ed. Philadelphia: Saunders, 1994:351. With permission.)

Given these considerations, it might be prudent to offer ASD closure via a limited inferior hemisternotomy incision in infants and small children, as well as possibly a trans- or subxiphoid approach in small children who typically have a relatively pliable thorax. Procedural safety, the likely need for peripheral cannulation and the potential to harm the growing breast tissue in small girls might further make an anterior approach preferable to a lateral thoracotomy in this age group. For cosmetic reasons, an inframammary approach should be offered to older girls and young women requiring ASD closure, whereas a limited anterior access should be considered as the procedure of choice for adolescent males and young men. Although considered in some centers, robotically assisted ASD closure is an attractive option. Surgeon's expertise with this particular approach must be weighted against the safety of conventional surgical intervention accomplished via the above-mentioned limited sternotomy or thoracotomy approaches.

## SURGICAL OUTCOMES

The postoperative course that follows correction of ASD and PAPVC is generally uneventful, and the majority of patients can be separated from mechanical ventilation in the operating room and discharged home within 3 to 4 days.[68]

Aside from morbidity that can be observed in any cardiac operation, specific minor early complications are represented by postpericardiotomy syndrome (typically 7–14 days

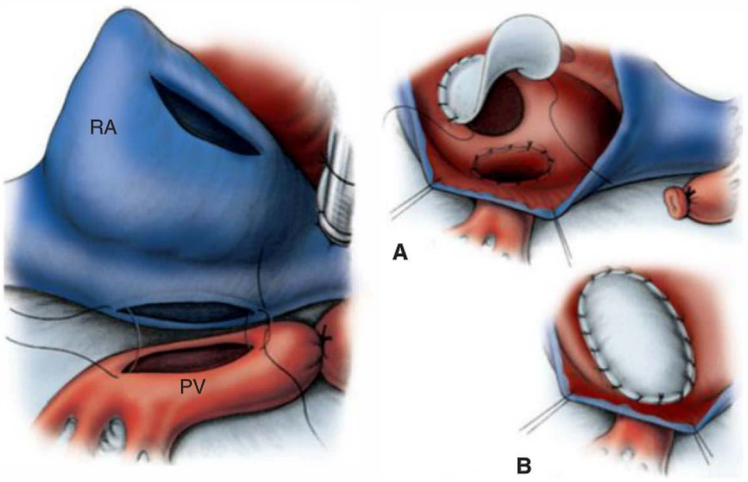



**FIGURE 64-19** Surgical correction of scimitar syndrome. When return of the anomalous pulmonary vein is very low, a side-to-side anastomosis can be constructed between the vein and the left atrium (left). Alternatively, the vein can be transected distally and anastomosed in an end-to-side fashion, with pericardial baffle rerouting to the left atrium (right). PV, pulmonary vein; RA, right atrium. (From Stark J. Secundum atrial septal defect and partial anomalous pulmonary venous return. In: deLeval M, Stark J (eds). *Surgery for Congenital Heart Defects*, 2nd ed. Philadelphia: Saunders, 1994:351. With permission.)

after the operation) and arrhythmias, particularly following SV ASD/PAPVC repair.[52,68]

Excellent long-term outcomes for patients of all ages have been reported[69–73] and, in the current era, morbidity and mortality for surgical closure of any type of ASD should approach zero.[30] Between 1993 and 2012, 277 children (age <18 years) underwent surgical ASD closure at our institution. Most patients had isolated secundum-type defects, 51 patients had SVD ± PAPVC, one infant had a CoS ASD, and three had SS; there was 1 operative death, due to PHT in a case of SS operated at 7 months of age, and no cerebrovascular accidents; the incidence of delayed pericardial effusions was 5 percent.

When surgery is indicated in smaller infants, mortality is similar (but not quite as low) as in older children, while reported morbidity ranges between 2.5 and 11 percent.[48,71,74]

## Percutaneous Closure of Atrial Septal Defects

Transcatheter ASD closure was first described in 1976 by King and coworkers.[75] In the subsequent 2 decades, multiple ingenious devices were developed to effectively close secundum ASDs. The goal has been to design a device that could be delivered through a small vascular sheath, produce complete closure in 98 percent or more of patients, be technically easy to insert, and remain removable until the point of final deployment. The Amplatzer Septal Occluder® (ASO) was introduced in 1995 and subsequently proven to be safe and effective in producing closure of OS ASDs, gaining FDA approval in November 2001 (Fig. 64-20). By the end of 2005, the manufacturer estimated that 80,000 implants had been performed worldwide. The ASO and the Gore Helix® device are the two devices currently approved for clinical use in the United States.

As part of the FDA approval process, a study of 596 patients was performed, with 442 undergoing ASO device closure of their ASDs and 154 having surgical repair of their defects.[76] Device implantation rate was 96 percent, with successful closure rate (<2-mm residual shunt) of 99 percent at 12 months. Patients undergoing catheterization remained in the hospital for 1 day on average (vs 3.4 days for surgical patients), and outcomes compared favorably with those of the surgical cohort.[77] Eligibility rates for device closure are much higher for older children and adults, with only 3.7 percent of all subjects enrolled in the initial FDA trial having ASDs that were judged inappropriate for device closure.

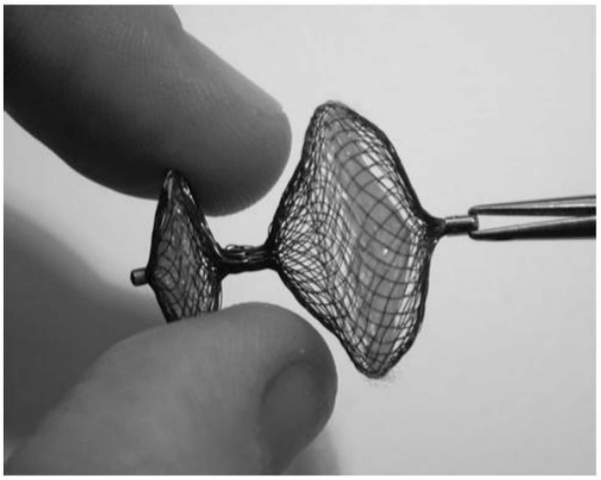


**FIGURE 64-20** Amplatzer atrial septal occluder device. (Courtesy of Dr. Richard Ringel, the Johns Hopkins University.)

Although closure of very large ASDs (greater than 30 mm) can be challenging, most defects are readily occluded using standard technique. Simultaneous use of fluoroscopy and TEE or intracardiac echocardiography is now standard practice and makes it possible to exclude from device implantation those defects with diminutive rims (<5 mm) or locations that would jeopardize valvular function or inflow and potential erosion. The procedure typically requires 60 to 90 minutes, with 10 to 20 minutes of fluoroscopy time. Overnight observation is strongly advised, with next-day discharge after echocardiographic confirmation of stable device position, minimal or no residual shunting, absence of pericardial effusion or interference with atrioventricular valve function or venous drainage. Postmarketing surveillance has identified 37 instances of device erosion (ASO) through the atrial wall into either the pericardial space or the ascending aorta, leading to hemopericardium and, in some cases, cardiac tamponade. Three deaths have been attributed to this phenomenon. A detailed review of all reported cases identified device oversizing and deficient retro-aortic (<5 mm) rim to be the greatest risk factors for device erosion.[78,79]

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## ATRIAL SEPTAL DEFECTS AND PARTIAL ANOMALOUS PULMONARY VENOUS CONNECTION BOARD REVIEW QUESTIONS (CHAPTER 64)

1. Which is correct regarding anatomy of ASD and PAPVC?
   - A. An OS defect occurs because of inadequate reabsorption of the septum primum.
   - B. An inferior SVD may promote left-to-right shunting without cyanosis.
   - C. The ostium of a CoS defect is invariably present along the posteroinferior margin of the triangle of Koch.
   - D. A superior caval ASD is located in the anterosuperior atrial septum, caudal to the superior limbic band.
   - E. In SS, the anomalous drainage passes vertically behind the hilum of the right lung.
2. Which is true regarding pathophysiology of ASD and PAPVC?
   - A. The location of the ASD has significant influence on the magnitude of the shunt.
   - B. If the ASD is restrictive, the $Q_p$:$Q_s$ will rarely exceed 2:1.

C. Mitral stenosis has no effect on flow across an associated ASD.
D. Heart failure in an infant is usually due to a large ASD.
E. The onset of pulmonary hypertension is predictable.

3. Which of the following is incorrect?
   A. An ASD less than 6 mm will almost always restrict spontaneously.
   B. An ASD between 6 and 8 mm may restrict even after age 5.
   C. An ASD over 8 mm may increase in size during childhood.
   D. The signs and symptoms of an ASD are not related to direction or magnitude of the shunt.
   E. An episode of paroxysmal atrial fibrillation may be the first presentation of an ASD in an adult.

4. Which is the most appropriate test prior to percutaneous closure of an ASD?
   A. TTE
   B. Three-dimensional TEE
   C. MRI
   D. Contrast CT scan
   E. Cardiac catheterization

5. Which is true regarding percutaneous closure of ASD?
   A. The Amplatzer device is the only FDA approved device.
   B. Successful closure was achieved in 95 percent of patients with the Amplatzer device.
   C. Eligibility rates for device closure are much higher in younger children.
   D. Success is defined as a residual shunt less than 4 mm.
   E. A deficient retro-aortic rim is a significant risk factor for device erosion.

## ANSWERS

1. **Answer: C.** The ostium of a CoS defect is invariably present along the posteroinferior margin of the triangle of Koch. An OS defect occurs when there is deficient development of the OP. An inferior SVD may promote right-to-left shunting with cyanosis. A superior caval ASD is located in the posterosuperior atrial septum, cranial to the superior limbic band. In SS, the anomalous drainage passed transversely and anterior to the hilum of the right lung.
2. **Answer: B.** If the ASD is restrictive, the $Q_p$:$Q_s$ will rarely exceed 2:1. The location of the ASD has little effect on the magnitude of the shunt. Mitral stenosis and other lesions that increase left atrial pressure can independently influence flow across the ASD. Heart failure in an infant is usually due to some other major condition rather than the ASD. The onset of pulmonary hypertension is variable and unpredictable.
3. **Answer: D.** The signs and symptoms of an ASD are strictly related to direction or magnitude of the shunt. An ASD less than 6 mm will almost always restrict spontaneously. ASDs between 6 and 8 mm may restrict even after age 5. An ASD over 8 mm may increase in size during childhood. An episode of paroxysmal atrial fibrillation may be the first presentation of an ASD in an adult.
4. **Answer: B.** Three-dimensional TEE is the most sophisticated test prior to percutaneous closure of an ASD.
5. **Answer: E.** A deficient retro-aortic rim is a significant risk factor for device erosion. The Amplatzer and Gore Helix devices are both FDA approved. Successful closure was achieved in 99 percent of patients with the Amplatzer device, defined as a shunt less than 2 mm. Eligibility rates are much higher in older children and adults.

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65

# Ventricular Septal Defects

*David L.S. Morales*
*Brandi B. Scully*
*Charles D. Fraser Jr.*

**KEY CONCEPTS**

- Epidemiology
  - Ventricular septal defect (VSD) is the most common noncyanotic cardiac anomaly (20 percent of all malformations); it is present in over 50 percent of children with complex congenital heart disease. VSDs occur in 0.5 of 1000 live births, and 5 percent are related to chromosomal syndromes.
- Morphology
  - VSDs vary in size, number, and location along septum. They are classified as (1) perimembranous (PM, most common), (2) inlet type, (3) nonmuscular outlet, and (4) muscular. The conduction system and aortic valve leaflets are in anatomic proximity and are at risk during repair.
- Pathophysiology
  - Degree and direction of shunting between the right and left ventricles depend on size (restrictive or nonrestrictive) and balance between the systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR). Aortic regurgitation can ensue as a consequence of leaflet prolapse through the defect.
- Clinical features
  - Small, restrictive defects are often asymptomatic. Symptoms of overcirculation are present in unrestrictive VSDs; with the development of irreversible pulmonary vascular changes in untreated large shunts, fixed pulmonary hypertension and cyanosis develop (Eisenmenger syndrome).
- Diagnosis
  - Echocardiography accurately defines the anatomy of VSD and associated lesions. Cardiac catheterization is rarely required.
- Treatment
  - Timing of closure is indicated by the degree of shunting and aortic valve involvement, and is most typically performed in infancy. Transatrial or transventricular approaches are most commonly utilized, with minimal morbidity and mortality. Percutaneous or periventricular device closure is still experimental, while a staged approach (with pulmonary arterial banding and delayed complete repair) is now considered only in selected cases.

## DEFINITION AND EPIDEMIOLOGY

A ventricular septal defect (VSD) is a deficiency in the ventricular septum that can vary in size, number, or location on the septum. All three determine its physiology, while the location alone determines its nomenclature. This is the most commonly recognized congenital heart defect excluding bicuspid aortic valve. Approximately 20 percent of patients with cardiac malformations have isolated VSDs and, if one includes VSDs in combination with other defects, VSDs are diagnosed in 50 percent of all patients with congenital heart disease.[1] VSDs occur at a rate of 0.5 per 1000 live births and in 4.5 to 7 of 1000 premature infants,[1,2] with a slightly higher prevalence in females (56 percent).[3] About 5 percent of VSDs are related to chromosomal syndromes (such as 22q11 deletion and trisomy 21), in which VSD is the most common cardiac defect identified.[4]

## HISTORICAL NOTE

In 1891, Dupren coined the term *Maladie de Roger* in honor of Henry-Louis Roger, who first described the clinical and pathologic findings of a VSD in 1879.[5] Eisenmenger then chronicled the natural history of an unrestrictive VSD by his account of the postmortem findings in a cyanotic patient

who died at age 32 with a large VSD, a severely hypertrophied right ventricle (RV), pulmonary valve (PV) and tricuspid valve (TV) insufficiency, and thickened pulmonary arteries (PAs).[6] However, the term *Eisenmenger syndrome* was not introduced until Abbott delineated the pathophysiology of a VSD in the 1930s.[7]

Muller was the first to surgically address a VSD in 1952 by placement of a pulmonary artery band (PAB).[8] Lillehei, using controlled cross-circulation (see Chapter 58), was the first to perform a VSD repair in 1954.[9] DuShane reported transventricular repair in 1956, while a transatrial approach was introduced the following year by Stirling.[10,11] Truex's description in 1958 of the atrioventricular node (AVN) and the conduction pathway in patients with VSDs is an integral part of all modern surgical techniques of VSD closure.[12] Kirklin and associates established in 1961 the ability to repair VSDs in small infants, therefore avoiding the two-staged approach of banding of the PA followed by VSD closure.[13]

## ANATOMY

In order to comprehend the different nomenclatures that are used for VSDs and the approaches and techniques for repairing this anomaly, one must understand the anatomy of the RV, the conduction system, and the TV.

The TV has three leaflets: septal, anterior, and posterior (Fig. 65-1). The posterior papillary muscles, which are located on the inferior wall of the RV near the septum, give rise to the chordae of the septal and posterior leaflets. The anterior papillary muscle gives rise to the chordae of the anterior and posterior leaflets. It is anchored at the acute margin of the RV and fuses with the RV muscle to become the moderator band, which travels inferiorly and becomes the septal band (alternatively termed trabecula septomarginalis or septomarginal trabeculation), which travels toward the RV outflow tract. The septal band then divides into its posterior and anterior arms. Between these two arms is the infundibular septum, also known as the conal, outlet, or supracristal septum. The medial papillary muscle (the muscle of Lancisi), which gives chordae to the anterior and septal leaflets of the TV, is most prominent and identifiable during infancy and attaches to the septal band or its posterior arm. The parietal band is the continuation of the septal band's posterior arm anteriorly onto the RV free wall. The parietal band and both arms of the septal band join to form the supraventricular crest (crista supraventricularis), the C-shaped nonobstructive entrance into the outlet region (subpulmonary conus) of the RV. This muscle shelf between the TV and PV creates PV–TV discontinuity.

It is essential to know the location of the AVN and the bundle of His in order to perform safe closure of a VSD. The AVN is located in the triangle of Koch (formed by the tendon of Todaro, the ostium of the coronary sinus, and the septal leaflet of the TV). More precisely, it is in the muscular region right below the triangle's apex and directly on the right atrial side of the central fibrous body. From another perspective, the AVN is under the nadir of the noncoronary (posterior) cusp of the aortic valve (Fig. 65-2). The AV bundle (bundle of His) arises from the AVN and exits at the apex of the triangle of Koch, passing to the ventricular side through the right aspect of the central fibrous body. At this point, the bundle is on the posteroinferior margin of the membranous septum, which lies just posterior to the commissure of the septal and anterior leaflets of the TV (Fig. 65-3). The bundle penetrates the ventricular septum and continues on the left ventricular (LV) side in 75 percent of patients. Whether on the right or left, it courses along the inferior border of the

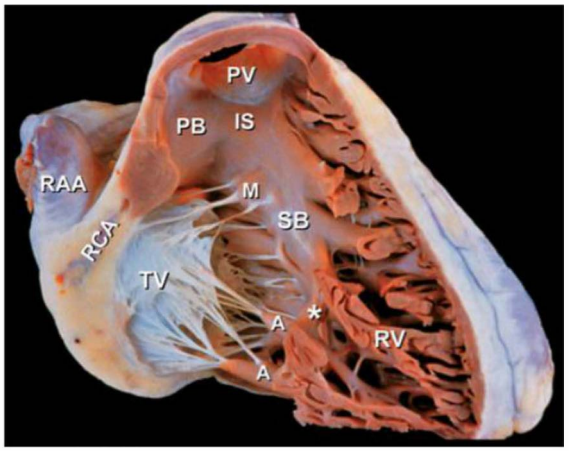



**FIGURE 65-1** Anterior view of the right ventricle in the anatomic position, as seen after removal of the anterior wall. *, moderator band; A, anterior leaflet of the tricuspid valve; IS, infundibular septum; M, medial papillary muscle of Lancisi; PB, parietal band; PV, pulmonary valve; RAA, right atrial appendage; RCA, right coronary artery; RV, trabecular portion of the right ventricle; SB, septal band; TV, tricuspid valve. (Reproduced with permission from Fuster V, Walsh RA, Harrington RA. *Hurst's the Heart*, 13th ed. www.accessmedicine.com. Copyright The McGraw-Hill Companies, Inc., all rights reserved.)

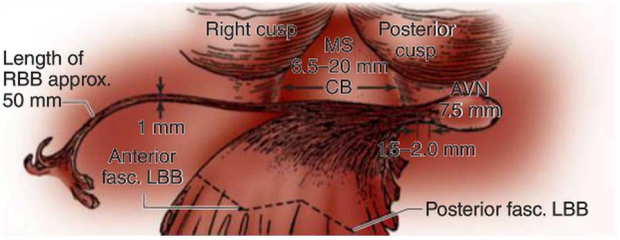



**FIGURE 65-2** A view of the atrioventricular conduction system from the left ventricle and its relationship to the membranous septum and the aortic valve. AVN, atrioventricular node; MS, membranous septum; fasc, fasciculus; RBB, right bundle branch; LBB, left bundle branch. (From Titus JL. Normal anatomy of the human cardiac conduction system. *Mayo Clin Proc* 1973;48:24–30. With permission.)

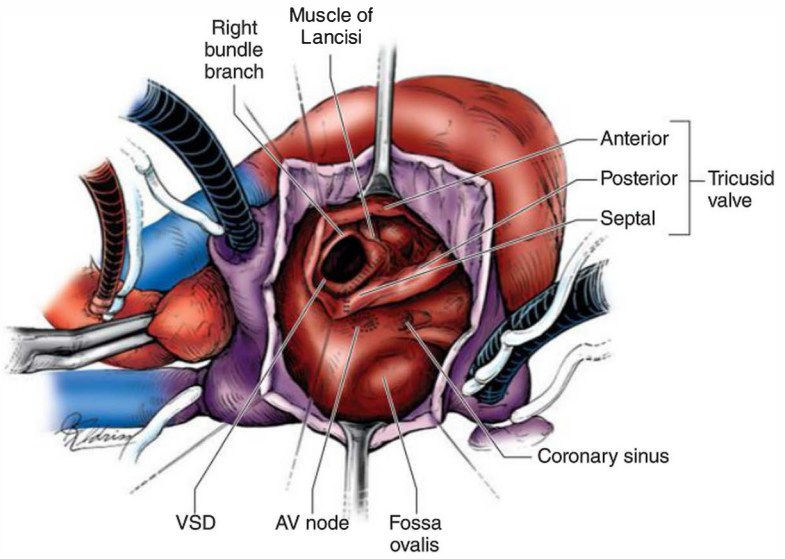



**FIGURE 65-3** Depiction of the atrioventricular node and its course on the inferior border of a perimembranous VSD; viewed from a right atrial surgical approach. (Drawing by Rachid Idriss. Used with the artist's permission, who reserves all rights. The drawing has not been modified; however, the labeling is that of the authors.)

membranous septum and begins to give off fibers to the left bundle branch over a distance of 1 to 2 cm. When the membranous septum is intact, this area is just below and to the left of the commissure between noncoronary and right coronary cusps of the aortic valve. In considering the bundle from the aortic valve perspective, one should imagine its path as coursing a few millimeters below the area between the right-noncoronary (posterior in Fig. 65-2) commissure and the nadir of the right coronary sinus. The remaining fibers of the bundle, which now surface to the anteroinferior border of the membranous septum, become the right bundle branch. The left bundle branch fans out over the septum while the right bundle branch courses as a single radiation (Fig. 65-3). From the anteroinferior border of the membranous septum, the right bundle passes below the muscle of Lancisi and then to the inferior borders of the septal and moderator bands until it reaches the anterior papillary muscle, where it disperses to innervate the RV. Therefore, the bundle of His is most often in harm's way during operations on a perimembranous (PM) VSD. The bundle of His runs along a PM VSD's inferior border from where it penetrates the TV annulus to the most inferior papillary muscle on the VSD's muscular rim (the muscle of Lancisi) (Fig. 65-4). The fact that the AVN and bundle of His are specialized myocytes and thus exist only in muscular tissue and not in fibrous tissue is an important fact to consider when placing sutures for VSD repair. The conduction system can also be at risk at the superior edge of a muscular inlet VSD, where the conduction system runs in the muscle between the VSD and the membranous septum.

## NOMENCLATURE AND PATHOLOGIC ANATOMY

There are many classifications of VSDs that have been proposed and used; our preference is a modification of the classic Anderson classification. However, to make our classification useful to the reader, we will compare other terms and classification to this terminology.

The ventricular septum can be sectioned into four regions: (1) the *inlet septum*, which is the area of the septum bounded by the attachments of the TV; (2) the *muscular septum*, which is the area from apex to the crista supraventricularis outside these attachments; (3) the *outlet septum*, which is the area from the crista supraventricularis to the PV, and (4) the *PM septum*, which is quite small and lies under the commissure of the anterior and septal leaflets of the TV. The muscular region is further subdivided into anterior, posterior, apical, and midmuscular regions. The Anderson classification names VSDs according to the region in which they are located. However, from a surgical perspective, one wants to know not only the location of the defect but also its relation to the conduction system. The latter can be transmitted to the surgeon by first defining whether the defect is PM (an absence of the membranous septum) or not (all other types of defects). This automatically tells the surgeon whether or not the conduction system is remote, and if not remote, where it is (inferior to a PM defect for a d-looped heart and superior to a PM defect for an l-looped heart, see Chapter 75). The exception to this rule is an inlet VSD, which is discussed below. One can also describe the type of PM VSDs by the areas defined

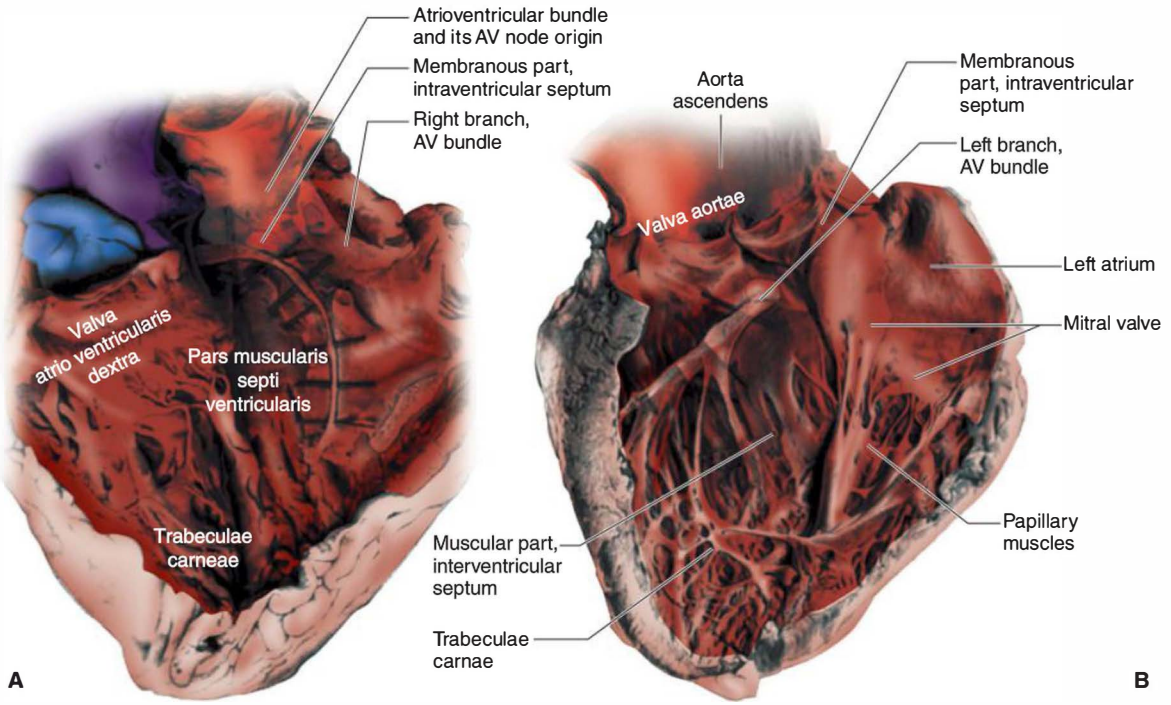



**FIGURE 65-4** Anatomy of the atrioventricular conduction system. **A.** The atrioventricular bundle and its right branch dissected in the right ventricle. **B.** The atrioventricular bundle and its left branch dissected in the left ventricle. (From Sobotta. *Atlas der Anatomie des Menschen*, 16th ed. Munich: Urban & Schwarzenberg, 1963. With permission.)

by Anderson. Therefore, a PM VSD can be one with muscular extension, outlet extension, inlet extension, or any combination. Non-PM VSDs can be muscular in type (outlet, inlet, anterior, posterior, apical, midmuscular) or outlet or inlet types bound by valve tissue (Fig. 65-5). The synonyms in other classifications for all the terms used above can be found in Table 65-1. The table lists all the different names by which a VSD within a certain region can be designated. The different names listed under a certain region are sometimes used imprecisely to denote any VSD in the area, but most of the terms are not interchangeable and refer to a very specific type of VSD. For example, some might use the terms *subaortic* and *supracristal* to refer to the same VSD; however, the former is a general term that refers to any VSD abutting the aortic valve, whereas the latter specifically refers to an outlet VSD abutting a semilunar valve.

The PM VSD represents approximately 80 percent of all VSDs; the remaining 20 percent are evenly distributed among inlet, outlet, and muscular VSDs. A notable exception to this distribution is the almost 30 percent overall prevalence of outlet-type VSDs in the Asian population with VSDs.[14] Small asymptomatic muscular VSDs, which are probably the most common heart defect (present in about 5 percent of all neonates), are grossly underestimated in these statistics, since the vast majority close in the first months of life without recognition.[15]

PM VSDs are intimately related to the TV and aortic valve. In fact, the absence of the PM septum often creates TV–aortic valve fibrous continuity. "Spontaneous closure" of PM VSDs usually occurs from partial or complete occlusion of the VSD by aneurysmal TV tissue. This aneurysmal tissue is formed from the sheer force of the left-to-right (L–R) shunt resulting in creation of fibrotic tissue, "accessory valve tissue," and/or, perhaps, remnants of endocardial cushion tissue. Some have described a defect of just the atrioventricular septum causing a shunt from the left ventricle to the right atrium, known as a "Gerbode defect."[16] When seen on echocardiography, this almost always represents a PM VSD with a jet directed through a cleft in the TV or the septal–anterior commissure, giving the echocardiographic appearance of a Gerbode defect. A consequence of this physiologic shunting from the LV to the right atrium can be extensive right atrial enlargement and, if an atrial septal defect exists, streaming of the blood can possibly cause right-to-left atrial (LA) shunting with resulting cyanosis.

Malalignment of the infundibular septum is also associated with PM VSDs, usually with outlet extension. If one considers the infundibular septum as being in the coronal plane with the RV outflow tract above and the LV outflow tract below, then comprehension of the malaligned VSDs is more straightforward. In an anteriorly malaligned VSD, the infundibular septum is deviated anteriorly into the RV

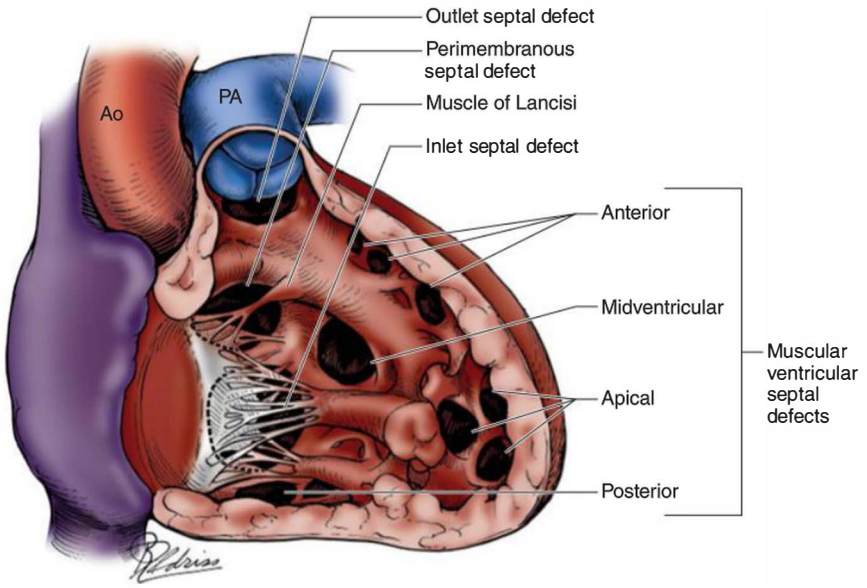



**FIGURE 65-5** The different types of VSDs as viewed via the right ventricle. (Drawing by Rachid Idriss. Used with the artist's permission, who reserves all rights. The drawing has not been modified; however, the labeling is that of the authors.)

outflow tract, causing obstruction. The aortic valve also moves anteriorly, so that it overrides the ventricular septum. In a posteriorly malaligned VSD, the infundibular septum deviates posteriorly into the LV outflow tract, causing obstruction.

**TABLE 65-1: Nomenclature Utilized for Ventricular Septal Defects**

| Preferred Terminology | Synonyms |
|---|---|
| **Perimembranous VSD** | |
| PM VSD with inlet extension | Membranous, infracristal, paramembranous |
| PM VSD with outlet extension | Membranous, conoventricular, subaortic |
| PM VSD with muscular extension | Membranous, infracristal, paramembranous |
| **Nonmuscular-outlet VSD** | Conal, supracristal, subarterial, subaortic, subpulmonary, infundibular, intracristal, doubly committed, conalseptal, juxta-arterial |
| **Inlet VSD** | Canal type, atrioventricular |
| **Muscular** | |
| Inlet | Canal type |
| Outlet | Conal, supracristal, subarterial, infundibular, conalseptal |
| Midmuscular VSD | Central |
| Apical muscular VSD | — |
| Anterior muscular VSD | Marginal |
| Posterior muscular VSD | Inferior |

Outlet defects are often differentiated between those that are completely bound by muscle and those that are bounded on one side by aortic valve tissue (subaortic, juxta-arterial VSDs), by PV tissue (subpulmonary VSDs), or both (doubly-committed, subarterial VSDs). This differentiation is useful in terms of the pathophysiology. The nonmuscular outlet defects along with PM VSDs with outlet extension can both be associated with aortic valve insufficiency, characterized by lengthening and eventual prolapsing of the right coronary leaflet (outlet defect) or noncoronary leaflet (PM VSD). This valve tissue can partially or completely close the defect. The conduction system is remote to outlet defects.

Inlet defects are beneath the septal leaflet of the TV, just inferior and posterior to the membranous septum. These defects can be an atrioventricular septal defect or a muscular inlet defect. The former is an endocardial cushion defect, characterized by absence of the PM septum, atrioventricular valve abnormalities, and a conduction system traveling along the inferior aspect of the defect. A muscular inlet defect is a VSD that can be remote to the conduction system or have the conduction system border the defect superiorly.

Muscular VSDs can be multiple or appear to be so because of the overlying trabeculae in the RV. This topography and multiplicity may cause difficulty in closure of these defects. When these impediments become prohibitive to conventional surgery, the term "Swiss cheese septum" is usually used to describe them. However, it should be noted that some believe that a Swiss cheese septum is actually an entity distinct from multiple VSDs. The morphology of the Swiss cheese septum is believed to originate from septal noncompaction during embryologic development; thus, unlike a group of muscular VSDs, Swiss cheese defects cannot close spontaneously.[17,18]

## PATHOPHYSIOLOGY

The pathophysiology of a VSD is determined by the size of the defect and its location. If the defect is smaller than the aortic annulus (a restrictive VSD), then the shunt's direction and volume is determined by the difference in systolic pressures of the ventricles. If the defect is larger than the aortic valve, then the defect is nonrestrictive and the pressure in the ventricles should equalize. The direction and volume of this shunt is determined by the difference in PVR and systemic vascular resistance (SVR).

Restrictive VSDs can be further categorized as small or moderate in size. A small VSD has a large resistance to flow, resulting in a small L–R shunt, and the pulmonary vasculature is well protected. The small shunt volume does not increase ventricular work or volume, and the LA and LV tend not to dilate. The large pressure gradient across the small VSD favors L–R flow throughout the cardiac cycle, which can produce a continuous murmur. Moderate-sized defects remain restrictive but allow a large enough L–R shunt to cause left-sided volume overload, characterized by LA and LV dilation. The pulmonary vasculature remains protected; however, some pulmonary hypertension can exist, which will cause RV pressure and work to increase. This results in mild RV hypertrophy.

Nonrestrictive VSDs allow for RV and LV to have equal pressures, with the determination of flow across the defect resulting from outflow resistance. In the LV, this is determined by SVR or by LV outflow tract anomalies (subaortic stenosis, aortic stenosis, coarctation, etc.). In the RV, this is determined by PVR or by RV outflow tract anomalies (PV stenosis, tetralogy of Fallot, etc.). PVR is high at birth and lessens the amount of L–R shunt; however, the PVR naturally decreases as the pulmonary vascular bed matures. The decline in PVR occurs mostly over the first few days, but the process is not completed until 2 to 6 weeks after birth.[19,20] The thinning of the vascular media, the enlargement and proliferation of the peripheral PAs, and the regression of the PA's perinatal muscularity mark the normal maturation of the pulmonary vessels. However, a large L–R shunt disturbs the growth and remodeling of the pulmonary vasculature, so that medial hypertrophy develops, muscularization of PA's persists, and the size and number of peripheral PAs is reduced. These structural changes are the basis of pulmonary vascular disease.[21,22] Any patient with a nonrestrictive VSD and no RV outflow tract obstruction has pulmonary hypertension, but this does not necessarily indicate that the patient has pulmonary vascular disease. The latter is a disease state of the pulmonary vasculature correlating to specific pathologic changes in the PAs, while pulmonary hypertension is simply a hemodynamic state of the PAs at any given time. A nonrestrictive VSD is characterized by a large L–R shunt, which will cause volume overload of the LA and LV, resulting in significant dilation of these chambers. This shunt will also result in pulmonary hypertension, which in time will cause RV hypertrophy and increasing PVR. As the PVR increases, the L–R shunt decreases. When end-stage pulmonary vascular disease ensues, the shunt can even reverse direction to a R–L shunt (i.e., Eisenmenger syndrome). Reversal of shunting and cyanosis rarely present in children below age 5 with isolated VSDs and is usually seen in adolescents and adults.

## CLINICAL FEATURES

The presentation of a patient with a VSD varies according to the size of the defect, the amount of L–R shunting, and PVR (Fig. 65-6). The majority of VSDs are small; these patients are asymptomatic and are diagnosed because of a loud systolic murmur, prompting an echocardiogram. The murmur is often not heard until the first postnatal visit, after PVR has dropped. Many of these defects will close spontaneously by muscle hypertrophy, fibrosis of the defect's margins, or leaflet adherence to the defect. In a study by Turner and colleagues, 290 children with isolated VSDs of all sizes were followed for a mean of 65 months.[23] The study revealed that 68 percent of VSDs with complete muscular borders closed spontaneously, while 29 percent of PM VSDs closed over the same time period. There were no cases of endocarditis in this nonoperative series. The aortic valve can also contribute to the narrowing of defects that have an outlet component, which can cause aortic insufficiency; this is a situation that demands prompt surgical treatment. Despite therapy, the natural history of the damaged aortic valve may no longer be normal. Thus waiting for spontaneous closure of PM VSDs or outlet VSDs, even with close follow-up, is not without risk.

Patients with large VSDs present with varying degrees of pulmonary overcirculation. The amount of overcirculation usually determines their age at presentation. Patients with larger defects and significant overcirculation can present in the first months of life, as PVR falls. These patients present with tachypnea, poor feeding, slow weight gain, and diaphoresis with activity. They are at risk for repeated upper respiratory tract infections, "cardiac asthma," and failure to thrive. Shunt size and the length of exposure to the resulting pulmonary hypertension will determine the time frame for the development of the varying degrees of pulmonary vascular disease. Patients with trisomy 21 have a shorter time course to reach significant pulmonary vascular disease than most children.[24] The end-stage of pulmonary vascular disease is termed Eisenmenger syndrome: PVR greater than SVR, reversal of shunt flow from L–R to R–L, cyanosis, and eventually RV failure.[25]

## DIAGNOSIS

### Physical Examination

Small defects usually have minimal physical findings and a normal chest x-ray (CXR) and electrocardiogram (ECG). Precordial activity is typically normal, but a thrill may be palpable on the lower left sternal border. The murmur is a

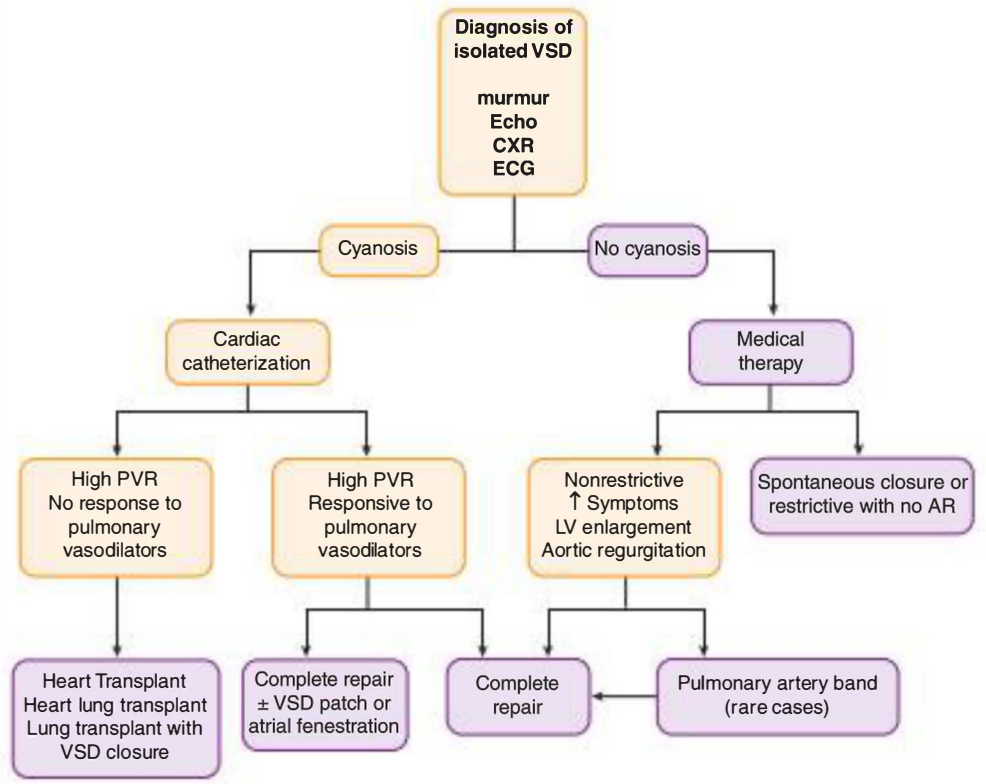



**FIGURE 65-6** Decision-making flowchart for isolated ventricular septal defect.

loud, high-frequency holosystolic murmur that includes and sometimes goes beyond the second heart sound and is heard best over the left lower sternal border. The murmur's continuous nature in systole provides evidence of a large pressure gradient between the RV and LV. Small muscular defects can sometimes have short murmurs that cut off at midsystole because of septal contraction.[26] Heart sounds are usually normal.

Moderate-to-large defects with minimal elevation of PVR present with similar exam findings that vary according to the amount of shunting. Precordial activity is accentuated and can span from the left apical area at first, indicating increased LV volume, to the right parasternal area eventually, indicating pulmonary hypertension and RV hypertrophy. As LV volume increases, the left thorax may begin to bulge, especially in younger infants. As the shunt increases, the third heart sound becomes more prominent, as does a middiastolic rumble, which indicates increased pulmonary blood flow at least double systemic blood flow. The holosystolic nature and the loudness of the murmur begin to dissipate as defects become larger and the pressure gradient between the RV and LV decreases. As pulmonary hypertension increases, the second heart sound has a narrower split and the pulmonary component becomes louder. There are no specific ECG patterns that are pathognomonic for VSDs and most patients' ECGs are normal. There can be ECG evidence of increased left heart volume (LA enlargement), but these findings are not specific to VSDs. On CXR, as the LV volume increases, there is a downward and leftward elongation of the cardiac silhouette on the anteroposterior (AP) film, whereas LA enlargement is seen on the lateral film or, when severe, by carinal widening on the AP film (Fig. 65-7). The increase in vascular markings denotes the amount of overcirculation.

Large VSDs coupled with high PVR allow for minimal shunting. Therefore, the LV work is close to normal, resulting in little precordial activity. There will, however, be a notable RV lift. A short or absent VSD murmur is usually heard. Murmurs that may be heard are a result of tricuspid regurgitation (TR) (harsh holosystolic murmur) or pulmonary insufficiency (PI) (early diastolic murmur). There is usually no third heart sound or diastolic rumble. The pulmonary component of the second heart sound is quite prominent; however, in over 50 percent of cases, the second heart sound is single. ECG may show RV hypertrophy. The CXR on these patients can demonstrate a normal-size heart or RV hypertrophy, both accompanied by marked prominence of the main PA and its immediate branches. There is a paucity of vascular markings on the outer third of the lung fields.

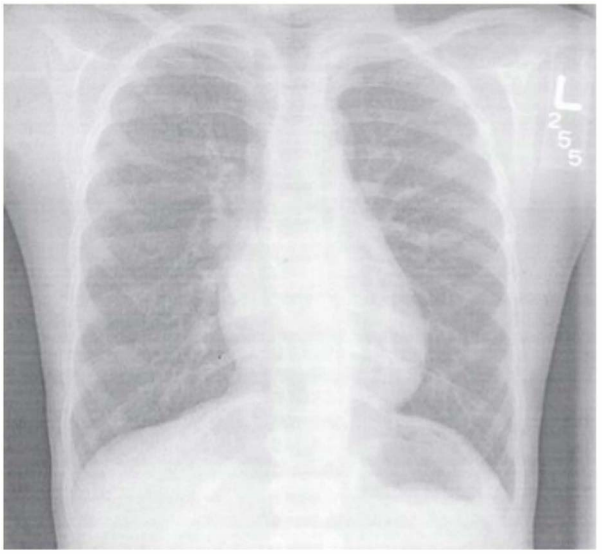


**FIGURE 65-7** Anteroposterior chest x-ray of a patient with a VSD. Note the leftward elongation of the cardiac silhouette, representing an increase in left ventricular volume, and the plethoric lung fields.

## Diagnostic Imaging

Two-dimensional echocardiography with color Doppler flow evaluation is the most widely used imaging to diagnose and characterize a VSD. To assess a VSD completely, one must not only localize it but also define its shape and dimensions, which is accomplished by viewing the defect from multiple imaging planes. Color Doppler allows for small VSDs not seen on two-dimensional echocardiography (usually <2 mm) to be identified and, more importantly, provides physiologic information about the VSD. One can measure the peak velocity across the VSD, which, if placed in the modified Bernoulli formula [4 × (peak velocity)$^2$], can yield the interventricular pressure gradient.[27] If this velocity is high, one has a restrictive VSD. If this velocity is low, one usually has a nonrestrictive VSD with near equalization of RV and LV pressures. However, at times a low velocity can be seen with a restrictive VSD if there is high RV pressure secondary to RV outflow obstruction or elevated perinatal PVR that has not yet fallen. Therefore, a low intraventricular pressure gradient does not necessarily correlate with pulmonary vascular disease, even in the presence of a nonrestrictive VSD. Right ventricular pressure may be estimated by measuring the velocity of the TR jet [4 (TR jet velocity)$^2$ + (central venous pressure) ≈ RV pressure]. If a PI jet exists, then an estimation of the diastolic PA pressure can be calculated by measuring its velocity [4(PI jet velocity)$^2$ + (RV diastolic pressure)]. One can also get a sense of where the patient is in the spectrum of VSD pathophysiology by assessing the amount of LV and LA dilation as well as RV hypertrophy. The echocardiogram should obviously seek other cardiac anomalies, in particular patent ductus arteriosus, aortic coarctation, and RV or LV outflow tract obstruction.

The principal indication for diagnostic cardiac catheterization of a patient with a VSD is when echocardiography and the clinical assessment indicate the possibility of advanced pulmonary vascular disease. Again, this would be rare for young children. One should keep in mind that the PVR of a child with an isolated VSD would have to be extremely elevated not to attempt a repair in this era of multiple pulmonary vascular bed dilators [inhaled nitric oxide (iNO), prostacyclin, sildenafil milrinone, etc.]. Therefore, one may question exposure to the risks of catheterization to quantify the echocardiographic findings more precisely when the results will not change the therapeutic decision. Catheterization of a VSD patient is also useful in attempting to define the anatomy of multiple apical VSDs, which magnetic resonance imaging (MRI) and echocardiography sometimes cannot identify. Catheterization of a patient with an isolated VSD should determine (1) a $Q_P$:$Q_S$ that can be estimated by (aortic $O_2$ sat—SVC $O_2$ sat)/(pulmonary venous $O_2$ sat—PA $O_2$ sat); (2) the calculated PVR = (mPAP—LA mean pressure) / pulmonary blood flow ($Q_P$) resulting in Wood units (mm Hg/L/min); (3) the PA pressures; (4) if PVR is high, the determination of the pulmonary vasculature reactivity to vasodilators such as 100 percent $FIO_2$ and iNO; and (5) the delineation of any unclear anatomy.

MRI has recently been used to provide accurate information about the morphology of VSDs. When surgical referral is being considered, MRI may be recommended in those patients in whom it is difficult to discern ventricular volume overload. The MRI can supply a noninvasive estimate of the $Q_P$:$Q_S$ as well as an accurate account of the heart's volumes and of associated anomalies that are sometimes difficult to diagnose by echocardiography (anomalous pulmonary venous return, for example). Also, three-dimensional intracardiac reconstruction MRI may soon be more widely available.

# THERAPEUTIC MANAGEMENT

## Medical Therapy

The medical treatment of VSD patients is aimed at decreasing L–R shunting and the symptoms of overcirculation. This is usually done with a combination of diuretics (i.e., furosemide), afterload-reducing agents (ACE inhibitors), and digoxin. Patients may also require nutritional support such as nasogastric tube feedings. Close surveillance for and aggressive treatment of upper respiratory infections is an important aspect of these children's care. Most children presenting with VSDs have some degree of pulmonary vascular disease; however, the presentation of an older cyanotic child with end-stage pulmonary vascular disease requires catheterization. The treatment and workup of such cases is outside the scope of this chapter. One should exercise caution when a patient requires intubation or inotropic support for a supposedly isolated VSD. Before embarking on surgical therapy, a careful investigation should be performed to make sure that no other cardiac anomaly (e.g., left-sided obstruction

or an additional source of L–R shunting) or primary pulmonary disease exists.

## Invasive Therapy

### SURGICAL THERAPY

Surgical techniques for VSD closure have progressed tremendously over the past 3 decades, and have allowed for neonatal surgical therapy to move from palliation to repair. At most institutions, all patients with isolated VSDs that require surgical correction undergo single-stage closure.

At the authors' institution, all repairs are generally performed with aortic and bicaval cannulation. Once the heart is arrested with cold cardioplegia, the right atrium is opened and the left heart is vented via the atrial septum. This should produce a bloodless and still intracardiac surgical field in which to work. There are several approaches to VSDs at this point, depending on the location.

The majority of VSDs (PM, inlet, and the majority of muscular defects) can be addressed via a right atrial approach (Fig. 65-8). The leaflets of the TV are retracted to visualize the defect. A particular variation in technique to visualize transatrially inlet defects or PM VSDs with outlet extension is the incision of the septal and/or anterior leaflet(s) of the TV via a radial incision or one parallel to the annulus. This will often provide excellent visualization for repair; once this has been completed, the TV is reattached to its annulus. The actual closure of the VSD can be done with a patch secured to the septum with interrupted pledgetted stitches, a running stitch, or a combination of the two. The patch can be made of various materials, including autologous pericardium tanned in glutaraldehyde, Dacron, or Gore-Tex. Primary (no patch) closure is usually reserved for a small muscular VSD or a windsock type defect in which the small effective orifice is surrounded by TV aneurysmal tissue. A key to successful VSD closure is the surgeon's awareness of the conduction system and the aortic valve. The TV annulus, which is the structure to which the VSD patch is often anchored posteriorly and superiorly, is just anterior to and sometimes in fibrous continuity with the aortic valve. Therefore, the aortic valve leaflets are at risk for injury when these superior sutures are being placed. The conduction system is at risk in stitching the inferior rim of a PM VSD between the muscle of Lancisi (the most inferior papillary muscle bundle on the VSD rim) and the TV annulus (Fig. 65-4). In this area, interrupted sutures can be taken far from the rim or a running suture can be placed very superficially along the rim. It is important to remember that the conduction system exists only in muscular tissue and not in fibrous tissue.

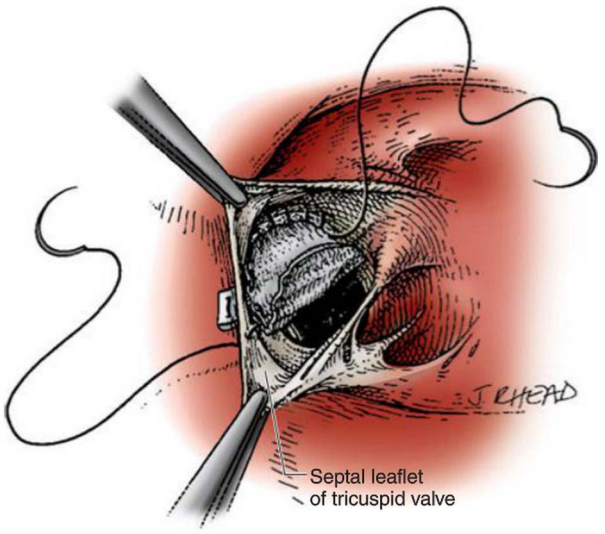



**FIGURE 65-8** Transatrial approach to VSD patch closure. In the illustration, a running suture technique is utilized. (Reproduced with permission from Kouchoukos NT, Blackstone EH, Doty DB, et al. (eds). *Kirklin/Barratt-Boyes Cardiac Surgery,* 3rd ed. Philadelphia: Churchill Livingstone, 2003:874. Copyright Elsevier.)

Approach through the PA is usually reserved for outlet defects. The pure outlet muscular defects can be closed with a simple primary or patch technique. However, the majority of outlet defects abut the PV annulus. These defects are also closed with a patch, but several unique factors must be considered. These particular VSDs have the highest incidence of significant aortic valve involvement. The aortic valve leaflets (usually the right coronary cusp) can prolapse and/or fill the defect. Therefore, it is essential to identify the aortic valve and not to include it in the repair. The patch will not only close the defect but also serve to support the aortic valve and eliminate the Venturi effect, which can be the cause of aortic valve prolapse. Some mild forms of aortic insufficiency will improve with repair of the defect alone, but this is unpredictable. If the aortic insufficiency is moderate or greater and/or the aortic leaflet clearly has a pathologic change, then the aortic valve should be addressed. PM defects can also be associated with aortic insufficiency and usually involve prolapse of the noncoronary cusp. A discussion of aortic valve repair techniques—which include triangular resection, subcommissural stitches, Trussler-type repair (horizontal plication of the redundant leaflet to the aortic wall), and Yacoub-type repair (primary closure of the VSD with vertical plication of the sinus and leaflet)—are beyond the scope of this chapter. There is no superior rim to outlet defects, so interrupted pledgetted sutures are usually placed through the fibrous base of the pulmonary valve leaflets and then through the patch. Interrupted or running sutures can anchor the remainder of the patch, with little concern for the conduction system, which is remote. However, if the posterior limb of the septal band (part of the crista supraventricularis) is not identified, the VSD may be a PM defect with outlet extension. Thus the conduction system would be on the inferior border of the defect.

A transaortic approach is usually applied in addressing a VSD that is associated with another left-sided lesion such as aortic valve insufficiency or valvular/subvalvular

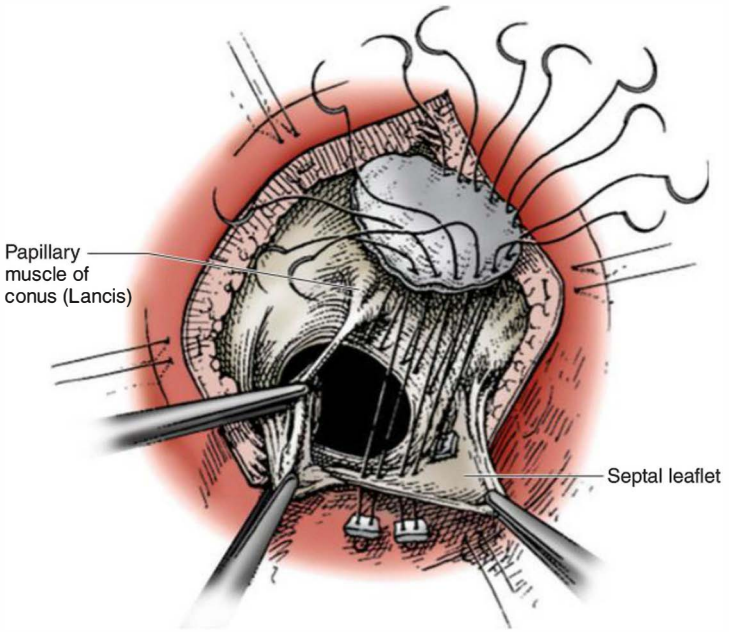



**FIGURE 65-9** Transatrial approach to VSD closure. In the illustration, an interrupted suture technique is utilized. (Reproduced with permission from Kouchoukos NT, Blackstone EH, Doty DB, et al. (eds). *Kirklin/Barratt-Boyes Cardiac Surgery*, 3rd ed. Philadelphia: Churchill Livingstone, 2003:876. With permission.)

stenosis. Our practice is still to close these defects from the RA approach to avoid left bundle branch block; however, many still use this approach, and discussion of it is helpful in contemplating the relationship of VSDs and the conduction system.

An RV approach (Fig. 65-9) for an isolated VSD is unnecessary except in very rare situations in which the VSD is inaccessible from the different approaches; for example: (1) When the posterior limb of the septal band is absent in a large outlet VSD, it is difficult to approach its inferior border from the PA or its superior border from the right atrium; thus neither approach suffices. (2) Visualization of a PM VSD with outlet extension can be hindered by hypertrophied infundibular muscle bundles. Resection of such bundles may at times be difficult from the RA or PA approaches; thus exposure is optimized by a small right ventriculotomy. Mapping out the ventricular incision in relation to the coronary anatomy is essential in avoiding significant ischemic complications, such as disruption of an anomalous anterior descending artery coming from the right coronary artery or of a large conal branch responsible for the proximal septal perforators. Again, we emphasize that right ventriculotomy is rarely needed to close an isolated VSD.

The LV approach is used even more infrequently than the RV approach and is reserved only for addressing those patients with multiple apical defects. Swiss cheese defects are difficult to approach from the right side because the trabeculations make the identification of distinct VSD borders impossible. However, this sieve-like defect on the right is well delineated on the nontrabeculated smooth septum of the LV. After careful mapping of the coronary arteries, an incision parallel and to the left of the anterior descending artery is started at the apex and extended vertically. These incisions are obviously avoided whenever possible because of pseudoaneurysms, ventricular dysfunction, and ventricular arrhythmias arising from scar tissue. These complications are why many authors still attempt closure of these Swiss cheese defects from the right side of the heart or with multiple VSD devices with a per-ventricular hybrid approach.

## RESULTS

### Surgical Outcomes

Complications from surgical VSD closure are infrequent; they include the following:

1. TV insufficiency from chordal shortening, leaflet entrapment by the VSD patch, or leaflet distortion if incised for exposure.
2. Possible aortic valve insufficiency if the sutures in the superior aspect of the patch catch or damage the aortic valve leaflets.
3. Complete heart block if the bundle of His is damaged or transected by sutures: Temporary block can occur secondary to edema in the area or trauma caused by careless

suctioning or manipulation around the AVN area with instruments. The decision of when to place a pacemaker depends on the individual situation. Factors in one's decision include preoperative AVN function, the nature of the procedure and cardiac anatomy, and the postoperative course. The frequency of this complication should be approximately 1 percent, and several centers have reported zero incidence of complete heart block postoperatively.[28–30] Right bundle branch block (RBBB), on the other hand, is a frequently seen rhythm change postoperatively (about 35 percent).[31]

4. Residual VSD: Leaving the operating room with a clearly significant residual VSD has been greatly reduced with the use of intraoperative transesophageal echocardiography (TEE). The difficulty arises when one must decide whether a small residual defect is physiologically and clinically significant enough to warrant rearresting the heart and attempting complete closure. A $Q_p$:$Q_s$ of less than 1.5:1 is used as a general guideline for a residual VSD shunt that could be observed. However, in practice, the decision to leave a residual VSD is multifactorial and based on such aspects of the case as the difficulty of the VSD closure, one's perception of how the heart will tolerate another arrested period, and the residual shunt that is left.

Operative mortality for isolated VSD closure is quite low, ranging from 0 to 3 percent.[32,33] The most common mode of death is acute cardiac failure, which is usually the result of one of the following: poor intraoperative myocardial protection, pulmonary hypertensive crises, a preoperative viral pulmonary process, or any combination of these with a small malnourished infant in heart failure. The risk factors for hospital death have changed significantly over the past decade. Young age, multiple VSDs, location, aortic insufficiency, PAB, and patient size, which all have been predictive of hospital mortality at various times in the past, are no longer risk factors.[31] In the current era, only major associated cardiac anomalies, especially when associated with multiple VSDs, are risk factors for hospital mortality. Preoperative PA pressures or resistance do not affect hospital mortality but do affect long-term results, which manifest as late deaths secondary to progression of pulmonary vascular disease.[34] Late mortality after repair, when pulmonary pressures are low, is less than 2.5 percent; most of these deaths result from ventricular arrhythmias.[31] The surgical repair of an isolated VSD before complications begin to arise (usually before 2 years of age, depending on the VSD) can return a patient to a normal life expectancy with full functional activity and normal growth.[31]

Scully et al. recently analyzed a cohort of patients with isolated VSDs over a 5-year period to determine the current expectations for VSD repair, which are that: (1) The patient will survive, (2) The operation will take an average of 4 hours, (3) The patient will be in the hospital for an average of 5 days, (4) The patient will have a very low risk (<1 percent) of adverse events, including complete heart block, extended hospital stay, arrhythmias, valve injury, depressed ventricular function, and (5) The risk of reoperation for a residual VSD is extremely low (<1 percent).[28] These are the expectations that can now be communicated to patients and their families.

## Device Closure

Device closure of VSDs is an emerging field that should be offered as a therapeutic option in very selected cases. These devices are usually introduced via percutaneous catheterization techniques but can also be positioned via a periventricular approach. The periventricular technique, which is performed off bypass and uses TEE guidance, passes an occluding device through the right ventricular free wall and deploys it.[35] This technique can be repeated for multiple muscular VSDs. Experience with percutaneous device closure is greatest with muscular defects. The two devices presently offered in the United States for closure of muscular defects are the Cardio-SEAL (NMT, Boston, MA) device (a modified ASD clamshell occluder, FDA-approved for high-risk surgical VSD patients) and the Amplatzer Muscular VSD occluder (AGA Medical, Plymouth, MN), a specifically designed nitinol wire with polyester mesh device, recently approved by the FDA. Clinical experience with percutaneous closure of muscular VSDs can be considered in the management of VSDs that are challenging to address surgically.

On the other hand, closure of PM VSDs using percutaneous device closure is still very much experimental, with only one available device (the Amplatzer Membranous VSD occluder, currently under study for patients weighing more than 8 kg). One recent study reported the immediate and midterm results of 100 patients in 24 international centers who underwent percutaneous device closure with the Amplatzer Membranous VSD occluder.[36] This study reported a 29 percent incidence of complications, with 13 patients experiencing rhythm or conduction anomalies postoperatively, and a complication rate of 58 percent for patients under 10 kg.[36] Xunmin and colleagues report equivalent results between device and surgical closure of PM VSDs.[37] Patients in this study, however, were greater than 2 years of age with a median age at device closure of 7.5 years. The young age and low weight of children who require early VSD closure due to heart failure, failure to thrive, and pulmonary hypertension remains a significant limitation for device closure. The challenge for this therapeutic approach is that PM VSDs are almost always surgically approachable with negligible mortality and minimal morbidity. Also, the possible complications for devices in this position include device embolization, air embolism, perforation, residual shunt and hemolysis in addition to heart block and aortic insufficiency.

## Palliation

The list of clinical and anatomic features that discourage early primary repair of VSDs becomes shorter with every year, and the number of cases in which surgical palliation for

isolated VSDs using PA banding has continued to decline. Size of the patient, which in the past was one of the most frequent reasons for a PAB, is no longer a contraindication for complete repair in major centers, where the expansion of neonatal heart surgery has rendered this consideration almost null. Successful repair in a premature neonate of 700 g has been reported.[38] In patients with isolated VSDs, a "Swiss cheese septum" and multiple VSDs are the most frequent diagnoses to be palliated with a PAB. PA banding is performed off bypass, can be approached either via a median sternotomy or a left thoracotomy, and is described in detail in Chapter 62. Placement of a PAB may not be necessarily a simple or low-morbidity procedure. It is not always straightforward to balance the pulmonary and systemic circulations, especially with a reactive and/or high PVR; PA banding can carry a hospital mortality of up to 8 percent and even higher in neonates.[39–41] It may require early reoperation for PAB adjustment; furthermore, 29 percent of PABs can be inadequate (too loose or tight)[37] and, after PAB removal, PA reconstruction is often required at the time of complete intracardiac repair.

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## VENTRICULAR SEPTAL DEFECTS BOARD REVIEW QUESTIONS (CHAPTER 65)

1. In which of the following patients could a diagnostic cardiac catheterization be an appropriate next step in management?
   A. A patient with clinical features and echocardiography compatible with advanced pulmonary hypertension
   B. A term infant with low birth weight and isolated VSD demonstrated on echocardiography
   C. A patient presenting in clinic with a holosystolic murmur
   D. Patient 3 days post repair of isolated VSD with RBBB
   E. Healthy child with echocardiographic, clinical, and radiographic evidence of VSD.

2. Which statement regarding surgical repair of isolated VSD is true?
   A. If complete heart block is present after repair, it is always permanent and placement of a pacemaker is indicated.
   B. Operative mortality for repair of isolated VSD remains at 3 percent in recent studies.
   C. There is no currently available transcatheter device closure of PM VSDs.
   D. RBBB is a relatively common result of VSD closure, occurring in approximately 35 percent of patients.
   E. Young age, multiple VSDs, and aortic insufficiency are all risk factors for death.

3. Which of the following is a possible consequence associated with waiting for spontaneous closure of an isolated PM VSD?
   A. Endocarditis
   B. Aortic insufficiency
   C. Pulmonary hypertension
   D. Failure to thrive
   E. All of the above

4. Which of the following is incorrect regarding outcomes after surgical repair of VSD?
   A. Operative mortality approaches zero.
   B. Risk of congenital heart block is less than 1 percent.
   C. Risk of valvular injury is less than 1 percent.
   D. Length of stay averages 3 days.
   E. The risk of reoperation for a residual VSD is less than 1 percent.

5. An infant with a loud, high-frequency holosystolic murmur heard best over the left lower sternal border presents with difficulty feeding. The patient is tachypneic and diaphoretic, and CXR reveals an enlarged heart. Which of the following would be an expected finding on echocardiography?
   A. LA dilation
   B. LV dilation
   C. An L–R shunt
   D. RV hypertrophy
   E. All of the above

## ANSWERS

1. **Answer: A.** As stated in the "Diagnostic Imaging" section of the chapter (page 1036), two-dimensional echocardiography with color Doppler flow evaluation is the most widely used imaging modality to diagnose and characterize a VSD, and is sufficient in most cases. A cardiac catheterization would only be indicated when echocardiography and the clinical assessment indicate the possibility of advanced pulmonary vascular disease.
2. **Answer: D.** As discussed in the "Results: Surgical Outcomes" section of the chapter (page 1039), RBBB is a frequently seen rhythm, occurring in approximately 35 percent of patients following VSD repair. Complete heart block is often temporary, secondary to edema in the area or trauma caused by instrument manipulation, and frequency of permanent heart block is approaching zero in most experienced centers. Operative mortality is also approaching 0 percent, and ranges from 0 to 3 percent. As discussed in the "Device Closure" section (page 1039), the Amplatzer Membranous VSD occluder is currently available for patients weighing more than 8 kg. Young age, multiple VSDs, and aortic insufficiency are no longer risk factors for death in this population.
3. **Answer: E.** As discussed in the "Clinical Feature" portion of the chapter (page 1034), patients with isolated VSDs can develop endocarditis, aortic insufficiency from the aortic valve prolapsing into the defect, pulmonary hypertension, the end stage of which is termed Eisenmenger's syndrome, where the PVR becomes greater than the SVR, and a reversal of shunt flow to R–L flow, cyanosis, and eventual RV failure, and patients with larger defects and significant overcirculation can present in the first months of life with slow weight gain, poor feeding, tachypnea, and diaphoresis with activity.
4. **Answer: D.** As discussed in the "Results" section of the chapter (page 1039), **A–C**, and **E** are all expected outcomes of surgical closure of isolated VSDs. Hospital length of stay remains longer than that for device closure, averaging 5 days.
5. **Answer: E.** As discussed in the "Diagnostic Imaging" and "Pathophysiology" portions of the chapter (page 1034), the size of an isolated PM VSD can be assessed by measuring the amount of LA and LV dilation as well as RV hypertrophy. A large L–R shunt would be expected in a patient with a nonrestrictive PM VSD.

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# 66 Atrioventricular Septal Defects

*Mazyar Kanani*
*Martin J. Elliott*

**KEY CONCEPTS**

- Epidemiology
  - The prevalence of atrioventricular septal defect (AVSD) is 0.19 per 1000 live births, accounting for 2.9 percent of congenital cardiac malformations. In about 60 percent of these cases, shunting is confined to the atrial level. Tetralogy of Fallot (ToF) is associated in 2 to 10 percent of cases of AVSD, while Down syndrome is seen in 75 percent of infants with complete AVSD.
- Morphology
  - This is variable, according to extent and presence of atrial and ventricular components; however, a common atrioventricular valve (AV) and displacement of the AV node are common features. These defects typically fall into three categories: (A) partial (primum component only); (B) complete atrial septal defect (ASD) and ventricular septal defect (VSD); and (C) transitional (restrictive VSD). Complete AVSD is further subdivided according to the degree of bridging of the superior leaflet. Although Rastelli type A is most common (70 percent of all complete AVSDs), type C is the one most frequently associated with ToF.
- Pathophysiology
  - Pathophysiology varies with the degree of shunting, left ventricular AV valve regurgitation, and pulmonary vascular resistance, as well as with associated anomalies.
- Clinical features
  - Larger left-to-right shunts (complete AVSDs) will present early in infancy with congestive heart failure and pulmonary hypertension, while presentation of partial and transitional AVSDs (in the absence of significant left AV valve regurgitation) will present later and have a similar presentation and natural history as ASDs.
- Diagnosis
  - Chest x-ray (CXR) will disclose an enlarged cardiac silhouette and increased pulmonary markings in large shunts. Echocardiography is diagnostic and defines type of defect, valvar morphology and degree of regurgitation, relative ventricular balance, and associated anomalies. Cardiac catheterization is used in selected cases and shows the characteristic "gooseneck deformity" from subaortic elongation of the left ventricular outflow tract (LVOT).
- Treatment
  - A staged approach [pulmonary artery banding (PAB) followed by complete repair] is relegated to selected cases of complete AVSD. Most cases should be repaired before 6 months of age, whereas partial defects without valvar regurgitation and defects with a restrictive VSD component can be repaired between 2 and 4 years of age.
- Outcomes
  - Operative mortality for complete AVSDs is currently below 5 percent, and incomplete defects have similar morbidity and mortality as ASDs. Long-term prognosis is defined by long-term valvar completenvy and associated lesions.

## INTRODUCTION

Following the first successful repair of atrioventricular septal defects (AVSDs) at the dawn of modern cardiac surgery, significant advances have been made in many aspects of overall patient management. In line with improvements in cardiopulmonary bypass, postoperative care, and refinement of surgical technique together with morphologic understanding,[1] there has been a striking reduction in both postoperative mortality and early morbidity.

Reflecting this increased confidence in the operative management in the last quarter century,[2] there has been an

evolution in the timing of surgery from a staged approach to an era of complete repair in early infancy (Fig. 66-1).[1,3]

## EPIDEMIOLOGY

The prevalence of AVSD has been put at 0.19 per 1000 live births, accounting for 2.9 percent of congenital cardiac malformations. In about 60 percent of these defects, the shunting is confined to the atrial level.

## Anatomic Considerations

The principal malformation that defines the AVSD lies at the atrioventricular (AV) junction. The normal arrangement is considered first.

### THE NORMAL ATRIOVENTRICULAR JUNCTION

The AV junction is defined as the muscular area that surrounds the orifices of the AV valves and marks the point at

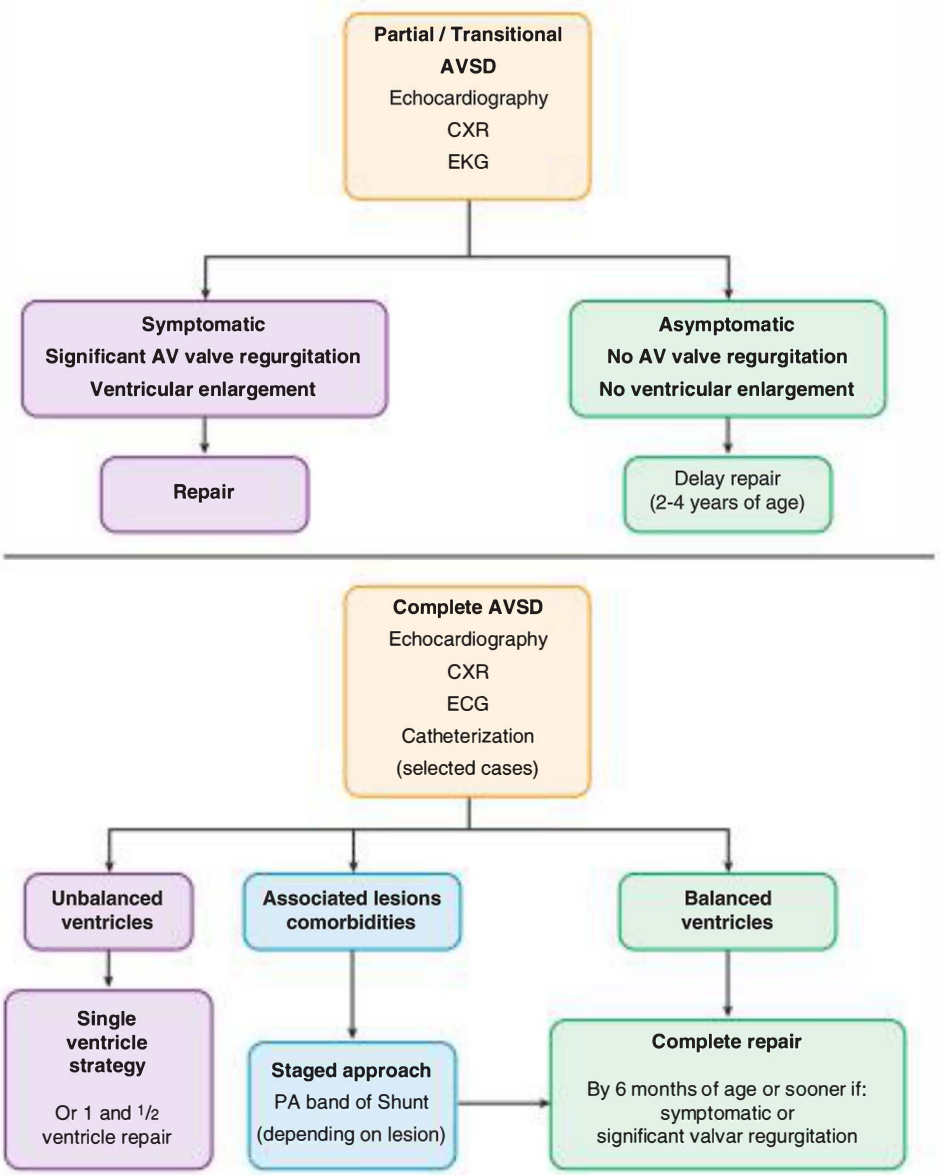



**FIGURE 66-1** Decision-making flowchart for atrioventricular septal defects (AVSDs). AV, atrioventricular; CXR, chest x-ray; ECG, electrocardiogram.

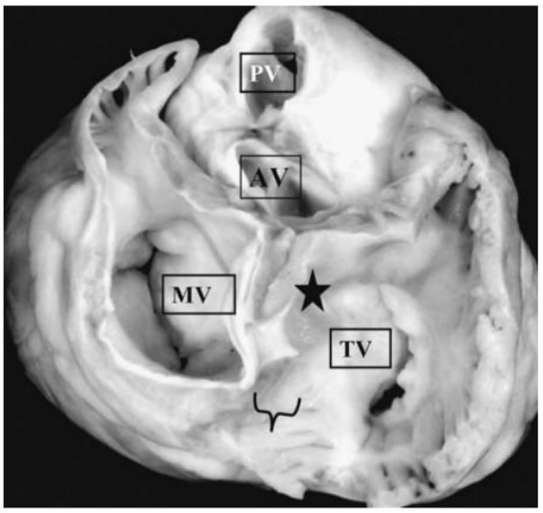



**FIGURE 66-2** The normal heart from above, with the atrial roof removed. There is normal atrioventricular septation, resulting in two separate atrioventricular junctions. The black star indicates the site of the atrioventricular septum that is bisected by the septal leaflet of the tricuspid valve. The black parenthesis is the position of the atrioventricular muscular sandwich. AV, aortic valve; MV, mitral valve; TV, tricuspid valve; PV, pulmonary valve.

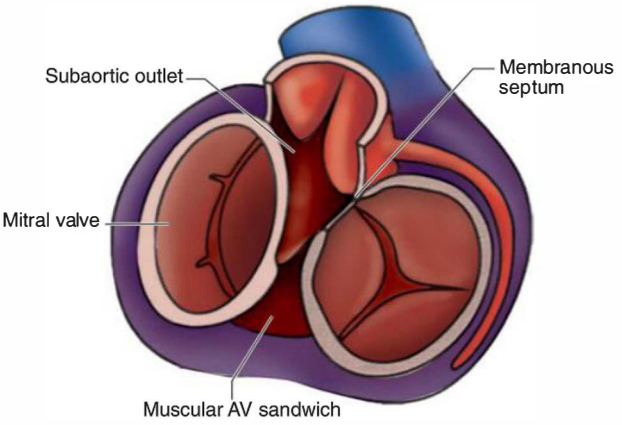



**FIGURE 66-3** A diagrammatic representation of the normally septated heart, showing the relationship between the subaortic outflow tract and the atrioventricular septum and sandwich. Note how the subaortic outflow tract is wedged between the two atrioventricular junctions. AV, atrioventricular.

which the distal margins of the atrial musculature meet the ventricular myocardium. Thus, there are two AV junctions in the normal heart, one supporting the tricuspid and the other the mitral orifices. Although the musculature of the two chambers abuts over the circumference of this junction, they are nevertheless separable apart from the area of the muscular axis of AV conduction—the bundle of His. Wedged in between the two junctions is the subaortic outflow tract, incorporating the indwelling aortic valve. Beyond this anteriorly is the subpulmonary outflow tract, mounted on its free-standing infundibulum (Fig. 66-2).

In considering junctional morphology, it is possible to distinguish the points of attachment of the AV valvar hinges from the points of muscular AV contiguity. At the right AV junction, where the hinges of the tricuspid valve are anchored by muscle throughout, these two areas are essentially the same apart from the short length where the septal leaflet of the valve crosses the membranous septum. In doing so, it divides the membranous septum into AV and interventricular components (Fig. 66-3).

This disparity between the muscular AV junction and the valvar annulus is most clearly seen at the mitral valve, where the fibrous tissue of the aortomitral fibrous continuity supports one-third of the annulus (Fig. 66-4).

## THE ATRIOVENTRICULAR SEPTUM AND "SANDWICH"

Observed in the four-chamber view, the tricuspid annulus is seen to lie at a more apical position than its mitral counterpart. Consequently, in the region immediately caudal and posterior to the area where the septal leaflet traverses the membranous septum, the muscular atrial septum overlaps the crest of the ventricular septum. This area between the offset hinges of the AV valves has previously been called the muscular AV septum,[4] but it is, in fact, none other than an extension of the fibro-adpose tissue of the posteroinferior AV groove (Fig. 66-5). The term *AV septum* should therefore be reserved for the AV component of the fibrous membranous septum. It is the absence of these two components—the fibrous membranous septum and the fibro-adipose muscular "sandwich"—that define hearts with AVSDs more than any other anatomic feature.

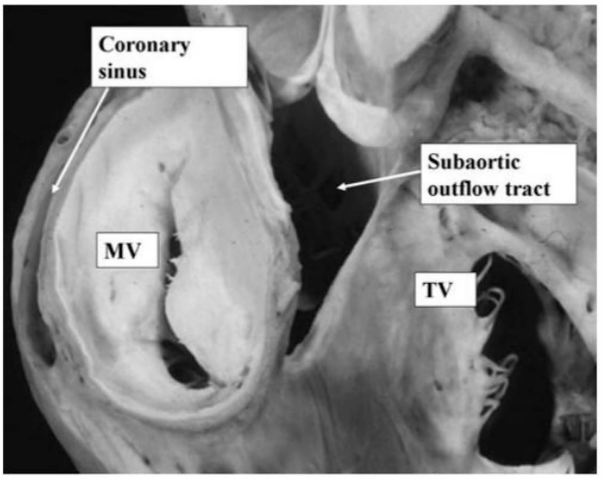



**FIGURE 66-4** A photographic equivalent of Fig. 66-3. The coronary sinus and circumflex branch of the left coronary artery skirt around the parietal left atrioventricular junction. MV, mitral valve; TV, tricuspid valve.

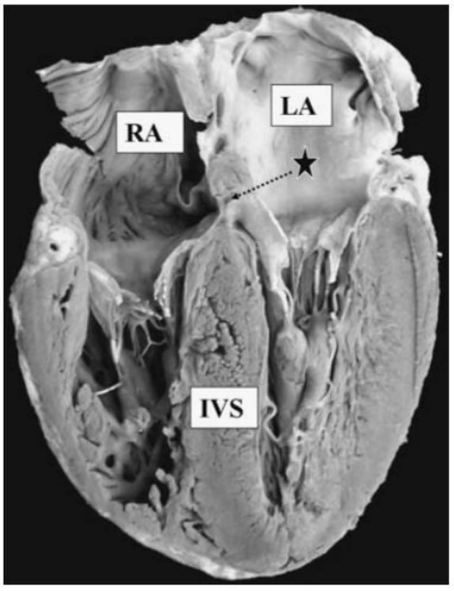



**FIGURE 66-5** A specimen of the normal heart taken in four-chamber section. The normal offsetting of the hinge points of the mitral and tricuspid valves gives rise to the atrioventricular septum (marked by the black star). IVS, interventricular septum; LA, left atrium; RA, right atrium.

## The Common Atrioventricular Junction in Atrioventricular Septal Defects

The common AV junction is the fundamental feature that sets the AVSD apart from the normal heart (Fig. 66-6).

It occurs irrespective of the number of valvar orifices and is seen even in the absence of septal deficiency. All other morphologic features seen in this defect arise as a direct consequence of this singular arrangement of the junctional structures. Other morphologic markers can be considered under the following subheadings:

- Leaflets arrangement
- Septal deficiency
- The ventricular mass
- The subaortic outflow tract
- The conduction axis

### LEAFLET ARRANGEMENT AND THE SUBVALVAR APPARATUS

The oval-shaped common AV junction in AVSDs surrounds an orifice guarded by a valve that usually possesses five leaflets. There is some variability in this arrangement, depending on the permutation of leaflet fusion. Variable fusion may result in separate right and left orifices or may produce any number of accessory orifices, depending on the location and extent of fusion.

Lying across the crest of the ventricular septum, to a variable extent, are the superior and inferior bridging leaflets (SBLs and IBLs). These were previously known as the anterior and posterior bridging leaflets, respectively, and have no counterparts in the normally septated heart (left in Fig. 66-6).

Adjacent to the SBL over the orifice of the right ventricle is the anterosuperior leaflet (ASL), which is analogous to its tricuspid counterpart. Supported by the parietal margins of the common junction on both sides are the right and left mural leaflets. The right mural leaflet lies against

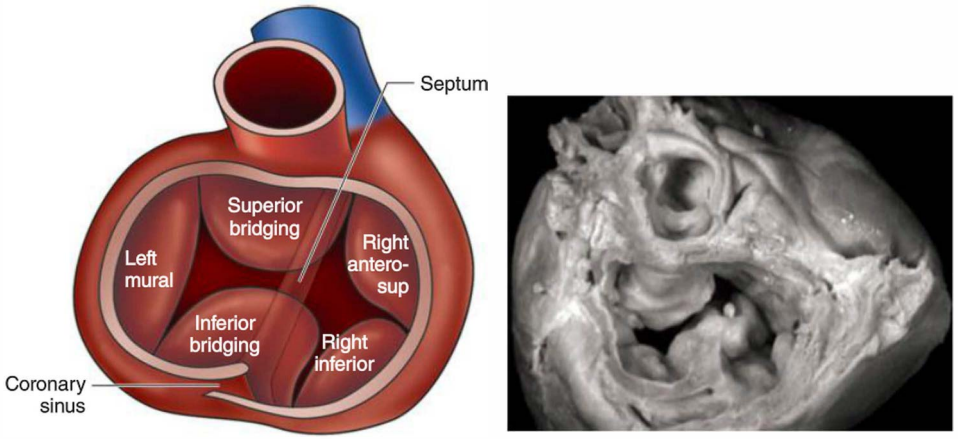



**FIGURE 66-6** Left: Schematic representation of a heart with atrioventricular septal defect and common atrioventricular junction, looking from the atrial aspect. The atrial roof has been removed. There is a common annulus that serves both ventricles, being surrounded by a common atrioventricular valve with five leaflets. The rightward black arrow indicates the position of the zone of apposition between the left sides of the superior and inferior bridging leaflets, which has previously been called a "cleft." Right: A photographic equivalent of the left panel. (Anderson RH, Becker AE. *Controversies in the description of malformed hearts*. London: Imperial College Press, 1997.)

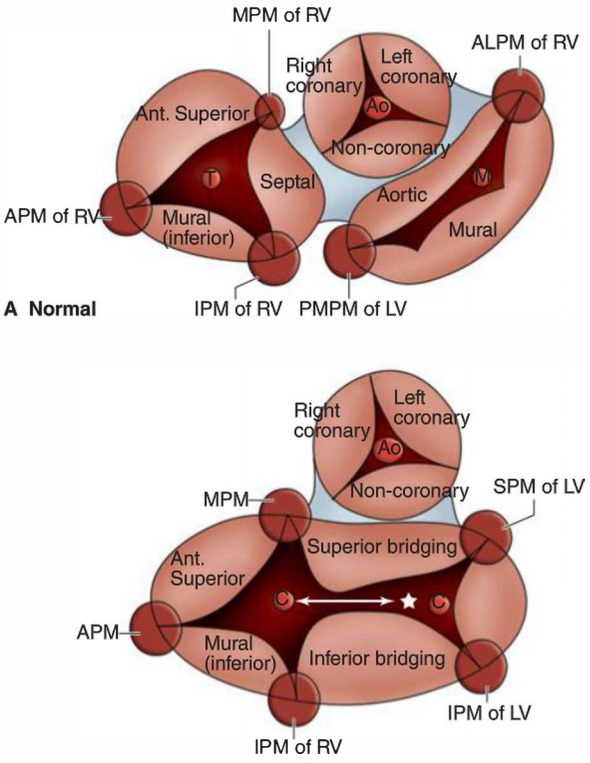



**FIGURE 66-7** Diagrams of the atrioventricular arrangement in the normal heart (**A**) and in the heart with deficient atrioventricular septation (**B**). View is from the ventricles (below). This shows not only the abnormal atrioventricular arrangement in atrioventricular septal defects but also the abnormal leaflet and papillary muscle positioning. ALPM, anterolateral papillary muscle; Ao, aortic orifice; APM, anterior papillary muscle; C, common orifice; IPM, inferior papillary muscle; LV, left ventricle; M, mitral orifice; MPM, medial papillary muscle; PMPM, posteromedial papillary muscle; RV, right ventricle; SPM, superior papillary muscle; T, tricuspid orifice. (From Anderson RH, Baker EJ, et al. *Pediatric Cardiology, vol 1*. Churchill Livingstone, 2001. With permission.)

the ASL and IBL, the left leaflet lies in apposition with the SBL and IBL.

The subvalvar apparatus is similarly abnormal, most importantly in the arrangement of the papillary muscles. The two left-sided papillary muscles normally lie obliquely, assuming anterolateral and posteromedial attitudes. In AVSD, these two muscles are located in the same vertical plane, being positioned superiorly and inferiorly; hence their names (Fig. 66-7).

The superior muscle supports the zone of apposition at the SBL–mural leaflet interface, and the inferior muscle supports the zone of apposition between the IBL and mural leaflets. Unlike the case on the right side, the position of these left-sided muscles is consistent. However, they may be found in clusters, as in the so-called parachute arrangement, where the chords from all leaflets converge onto only one papillary muscle (Fig. 66-8).

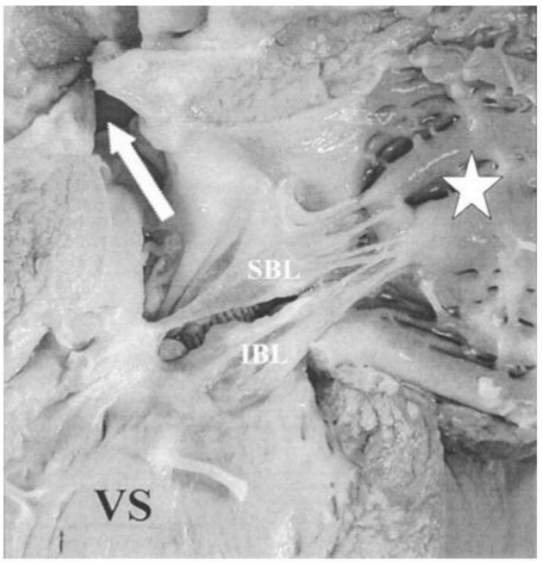



**FIGURE 66-8** A specimen of atrioventricular septal defect looking from the left ventricular aspect. There is a solitary papillary muscle arrangement in which the superior (SBL) and inferior (IBL) bridging leaflets converge to a single papillary muscle (white star). The white arrow indicates the position of the subaortic outflow tract. VS, ventricular septum.

## RASTELLI CLASSIFICATION AND RIGHT VENTRICULAR PAPILLARY MUSCLES

The papillary muscle arrangement of the right side depends on the degree of bridging of the SBL across the VSD. This forms the basis for the Rastelli classification.[2,5]

When there is minimal bridging of the SBL into the left ventricle, or Rastelli class A, the edge of the leaflet is tethered to the crest of the septum (Fig. 66-9A). Here, the ventricular septum is analogous to a papillary muscle, supporting the zone of apposition between the SBL and IBL. In this situation, the ASL of the right AV valve is well developed and morphologically similar to its tricuspid counterpart. At operation, this arrangement gives the appearance of the SBL being divided over the septum (Fig. 66-10A). Subsequent anatomic observation determined that this "division" of the SBL over the septum merely represents the zone of apposition between the SBL and well-formed ASL in the class A defect and that the SBL is undivided over the ventricular septum in all classes of the defect.[6–8]

In the class B defect, the SBL extends even more into the right ventricle, with further reduction in the size of the ASL (Fig. 66-10B). It is usually unattached to the ventricular septum but at its right margin is supported solely by an anomalous right ventricular papillary muscle that arises from the septomarginal trabeculation. In the so-called type C defect (Fig. 66-9B), the SBL extends even further into the right ventricle and floats freely above the ventricular septum, extending from the anterior papillary muscle of the right ventricle to the superior papillary muscle of the left ventricle (Fig. 66-10C). The ASL is necessarily smaller,

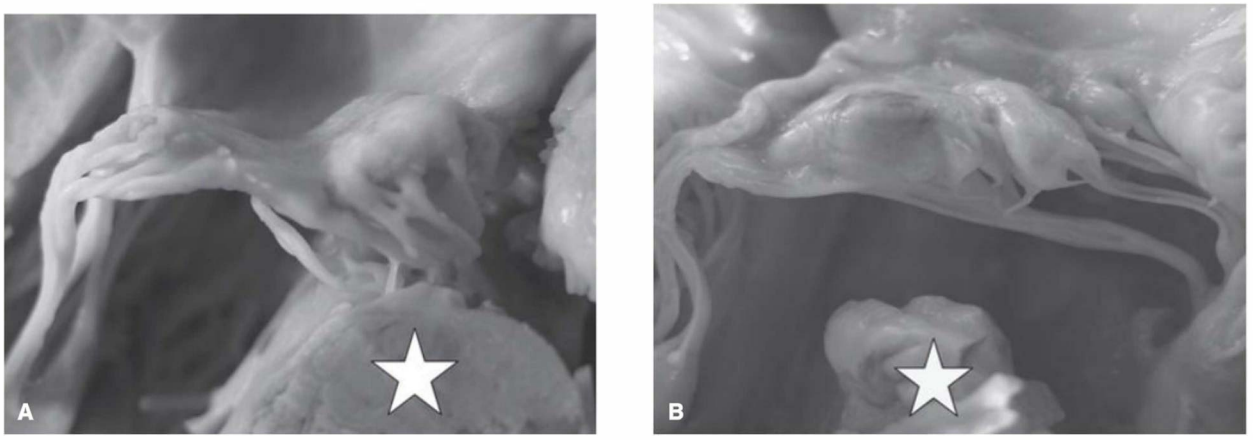



**FIGURE 66-9** Specimens showing variations in the degree of bridging of the superior bridging leaflets, forming the basis of the Rastelli classification. This is a four-chamber orientation; the white stars indicate the position of the ventricular septum. **A.** Rastelli type A arrangement where the SBL is minimally bridged and bound to the crest of the ventricular septum. **B.** The type C arrangement where the superior bridging leaflet bridges the septum to the greatest extent and floats freely. (Rastelli GC, Ongley PA, Kirklin JW, et al. Surgical repair of the complete form of persistent common atrioventricular canal. *J Thorac Cardiovasc Surg* 1968;55:299–308.)

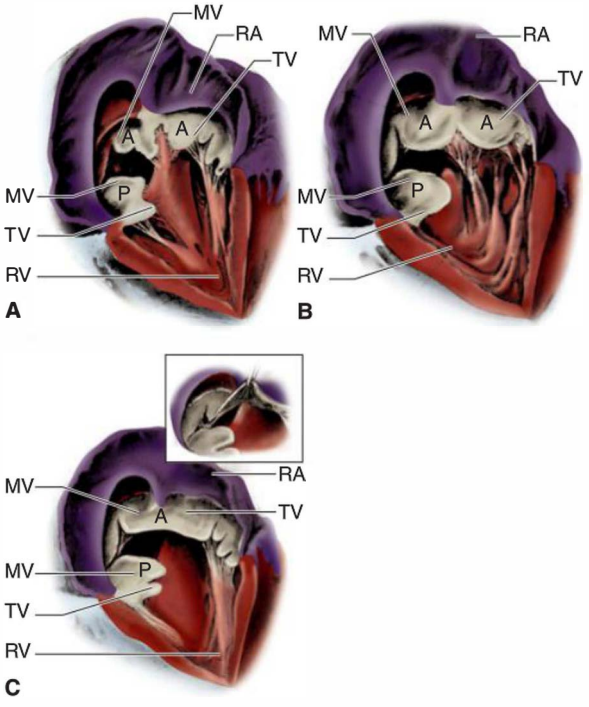



**FIGURE 66-10** Figures taken from Rastelli's original study on the arrangement of the superior bridging leaflet in atrioventricular septal defects (**A–C**). In (**A**), the superior bridging leaflet is minimally bridged, with most of the leaflet confined to the left ventricle and tethered to the septum. In (**B**), the degree of bridging is greater, with its right ventricular attachment being to an anomalous papillary muscle. In (**C**), the leaflet is maximally bridged, being free-floating and attached onto the medial papillary muscle of the right ventricle with the anterosuperior leaflet. (From Rastelli G, Kirklin JW, Titus JL. Anatomic observations on complete form of persistent common atrioventricular canal with special reference to atrioventricular valves. *Mayo Clin Proc* 1966;41:296. With permission.)

accommodating the greater encroachment of the SBL into the right side. Lack of chordal attachments to the septum ensures unhindered access to the aortic valve beneath.[9,10] In the type C defect, there is a high association with tetralogy of Fallot (ToF). The reasons for this are developmental, as rightward displacement of the outlet septum during the development may limit chordal attachment to the septum.[11,12]

Epidemiologically, the type A defect has the greatest prevalence, both in morphologic and clinical series, ranging from 50 to 75 percent of cases.[7,13–15] Variability in the degree of bridging of the SBL may also be seen in cases of AVSD with separate orifices, or the "partial defect," where minimal bridging of the SBL is the most common pattern.

## THE NATURE OF THE ZONE OF APPOSITION: "CLEFT" OR "COMMISSURE?"

The area between left sides of the bridging leaflets has been the subject of much controversy. The principal question is whether it represents a cleft, as in the so-called isolated cleft of the anterior leaflet of the mitral valve,[16] or whether it is the commissure between the leaflets of a left AV valve. A commissure is the functional division between the leaflets of a valve that is supported by a fan-shaped tendinous chord atop a papillary muscle. A cleft is defined as a space or opening made by splitting the anterior leaflet.[17] Given these definitions, this space between the bridging leaflets may be best thought of as septal commissure in a trifoliate leaflet AV valve.

## MORPHOLOGY OF THE ATRIAL AND VENTRICULAR SEPTAL DEFECTS

Although septal deficiency is almost uniformly seen in hearts with this defect, the pattern of blood flow between the chambers is largely determined by the chordal and leaflet anatomy.

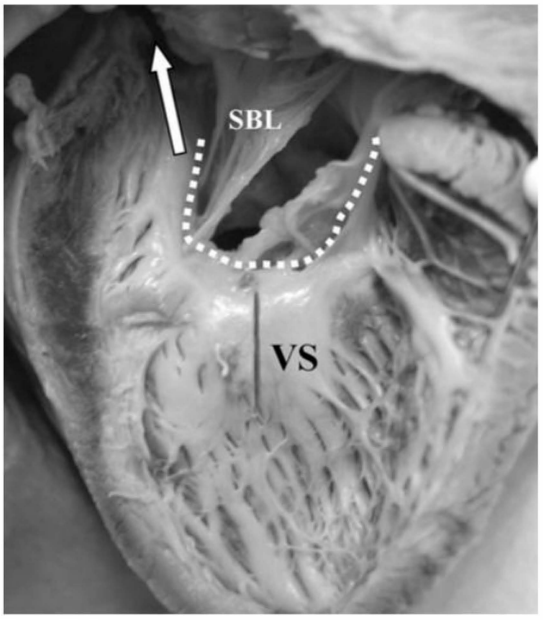



**FIGURE 66-11** A specimen of atrioventricular septal defect looking from the left ventricle in long-axis section. The "scooped out" appearance of the crest of the ventricular septum (VS) has been marked by the white line. The white arrow points to the narrowed subaortic outflow tract. SBL, superior bridging leaflet.

The ventricular septum in AVSD is "scooped," with a gentle curve extending from the crux of the heart to the left ventricular outflow tract (LVOT) (Fig. 66-11). The depth of the scoop and the resulting deficiency are very variable, being more extensive in hearts with common orifices.[7,18,19]

Above the plane of the annulus is the so-called ostium primum defect (Fig. 66-12), which, in some instances, may be obliterated through attachments of the leaflets to its edge, giving rise to obligatory ventricular shunting. If combined with a secundum atrial septal defect (ASD), it may produce a common atrium.

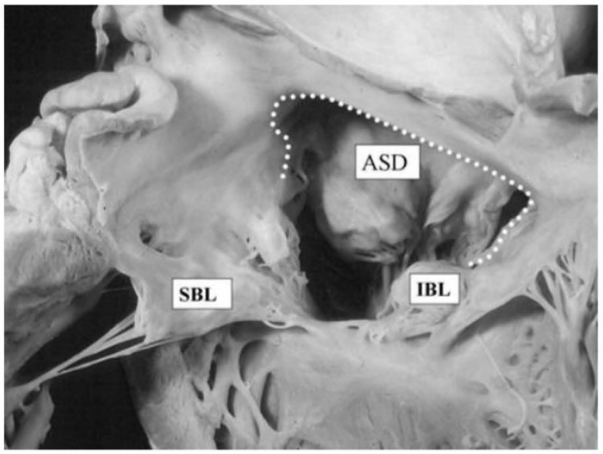



**FIGURE 66-12** Specimen of atrioventricular septal defect looking from the left ventricle, showing the relationships between the atrial septal defect (ASD), ventricular septal defect, and bridging leaflets (SBL and IBL). The white line shows the characteristically crescentic shape to the primum ASD component.

## COMMON VERSUS SEPARATE ORIFICES

There are two varieties of AVSD, depending on the level of intra-cardiac shunting caused by the pattern of leaflet fusion. However, when the leaflets are stripped from both variations, their junctional morphology is identical.[4]

In the defect with separate orifices, also known as the partial AVSD, there is a tongue of leaflet connecting the bridging leaflets over the ventricular septal crest. Therefore, the septal communication beneath the leaflets is obliterated, limiting shunting to the atrial level (Figs. 66-13 and 66-14).

Although this fusion results in separate AV orifices, the connecting tongue is not a continuation of the common annulus across the septum. The morphologic extent of this tongue again shows variability. In some instances, the bridging leaflets are fused with each other, but multiple interchordal spaces beneath the leaflets leave the potential for interventricular shunting (Fig. 66-15).

Hearts exhibiting this latter phenomenon have been termed the "intermediate" or "transitional" AVSD, emphasizing separate orifices in the context of persisting ventricular shunting, as if it were embryologically a transitional form between two extremes. We believe that this term is misleading and loses sight of the fact that the defining feature of hearts with this defect is deficiency of AV septation and not leaflet morphology. As such, septation may be deficient

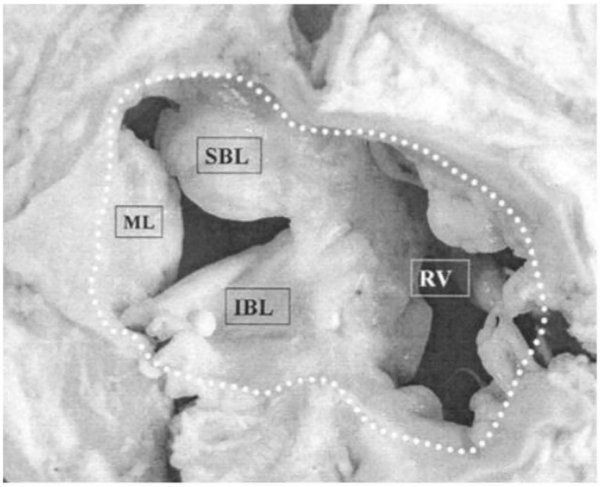



**FIGURE 66-13** A specimen of atrioventricular septal defect with common atrioventricular junction (encircled by the white line) but with separate orifices. The orifices are divided by a connecting tongue of tissue between superior and inferior (SBL and IBL) bridging leaflets, which is also bound to the crest of the ventricular septal defect. This closes off the ventricular communication. ML, mural leaflet of the left atrioventricular valve; RV, right ventricle.

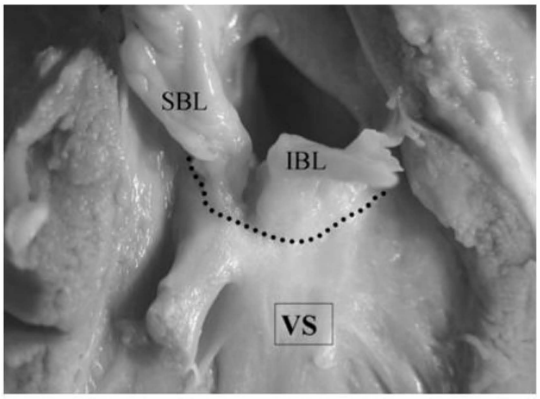



FIGURE 66-14 Specimen of atrioventricular septal defect with separate orifices, looking from the left ventricle. The dotted line shows the position of the crest of the ventricular septum (VS), which is bound to the bridging leaflets (SBL and IBL), thus closing off any ventricular communication. Note how the zone of apposition has a three-dimensional configuration in that it rises up from the septum before continuing forward.

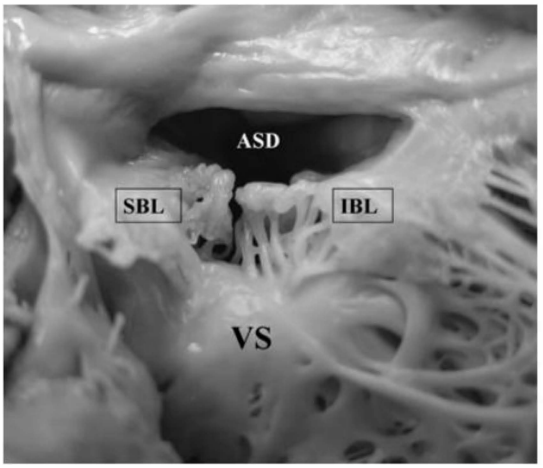



FIGURE 66-15 Specimen of atrioventricular septal defect, looking from the left ventricle. This is a defect with a common orifice, but there are multiple small inter-chordal communications between the ventricles. This has previously been called the "intermediate" or "transitional" defect.

or otherwise, with no intermediate arrangement.[20] Despite the clinically more benign course of the defect with separate orifices, there is a greater prevalence of subaortic obstruction, papillary muscle anomalies, and leaflet dysplasia. Nevertheless, the association with other complex malformations is more common in hearts with a common orifice.

## VENTRICULAR MORPHOLOGY AND BALANCE

In the normal heart, the inlet/outlet ratio is the same (Fig. 66-16, left panel). This is also seen in hearts with perimembranous VSDs and those with an isolated "cleft" in the anterior leaflet of the mitral valve, which have all been previously described as the "forme fruste" of AVSD.[21] In the latter, the outlet length is significantly longer than the inlet and can be appreciated from the "gooseneck" deformity of the subaortic outflow tract (Fig. 66-16, right panel). This has been explained in terms of a shorter inlet[22] or a longer outlet.[23] These ratios are the same in AVSDs with common and separate orifices.

The diameters of the inlets of both ventricles as well as the volumes of the ventricles are the same, or balanced, with the atrial and ventricular septa being in line. In the era of two-staged repair, a reduction in the volume of the right



FIGURE 66-16 Left-hand panel: The comparable inlet and outlet dimensions of the normal heart. Right-hand panel: The inlet dimension of the heart with the atrioventricular septal defect, which is much smaller than the elongated outlet. This accounts for the scooping of the ventricular septum.

ventricle was occasionally observed after pulmonary trunk banding, owing to hypertrophy of the trabecular layer of the myocardium. Aside from this specific situation, left dominance may occur with hypoplasia of the right ventricular and pulmonary arterial components, typically in association with malalignment of the atrial and ventricular septa. This leads to the most extreme case of double-inlet left ventricle with common AV valve.[24] In the case of right dominance, there is usually hypoplasia of the left ventricular and aortic structures, with normal alignment of the atrial and ventricular structures.[25]

## THE SUBAORTIC OUTFLOW TRACT AND SUBAORTIC STENOSIS

Although the subaortic outflow tract is narrower[26] and longer[10] than normal (as seen on angiography), obstruction is surprisingly uncommon (Fig. 66-16, right panel).[27]

The principal source of obstruction derives from the anterior and unwedged position of the subaortic outflow tract, which is a direct product of failure of AV septation. This exaggeration of the subaortic outflow tract is also more pronounced in hearts with the Rastelli type A leaflet morphology, where the SBL is tethered to the crest of the ventricular septum, narrowing the outflow tract even further. This also explains why obstruction is more frequent in the setting of separate orifices.

In addition, the superior papillary muscle or an anomalous portion of it may extend into the subaortic outflow tract, or there may be a prominent anterolateral trabecular muscle bundle. Similarly, there may be accessory tissue tags or chordal attachments from the SBL, further obstructing the path. Such hearts may also become obstructed through mechanisms that affect normally septated hearts, such as fibrous subaortic shelves.

There may also be a further, dynamic component to the potential for obstruction in these hearts. The elongated outflow tract is a muscular tube that constricts during systole, heard as a persisting systolic murmur in the absence of clinically significant left AV valve regurgitation. Obstruction is also well recognized in the postoperative setting, as after left AV valvar replacement, where it accounts in part for the high mortality.

## THE MORPHOLOGY OF THE ATRIOVENTRICULAR CONDUCTION AXIS

The displacement of the conduction axis is the direct result of deficient septation, with absence of the central fibrous body that normally marks the point at which the AV node continues as the AV bundle. There is some variability among hearts with the AVSD, depending on the alignment of the atrial and ventricular septa. Thus, the nodal triangle is displaced posteriorly and inferiorly and lies in the posterior right atrial wall, between the orifice of the coronary sinus and the crux of the heart.

From this position, the bundle of His passes to the crest of the ventricular septum through the crux, which is the first point of contact of the atrial and ventricular musculature. It runs along the crest of the septum under the cover of the IBL, giving off left bundle branches. At about the midpoint of the ventricular septum, it becomes the right bundle branch, which descends to the medial papillary muscle of the right ventricle (Fig. 66-17). Thus, at operation, the greatest danger is at the time of securing the atrial septal patch, when the node is approached at the crux.

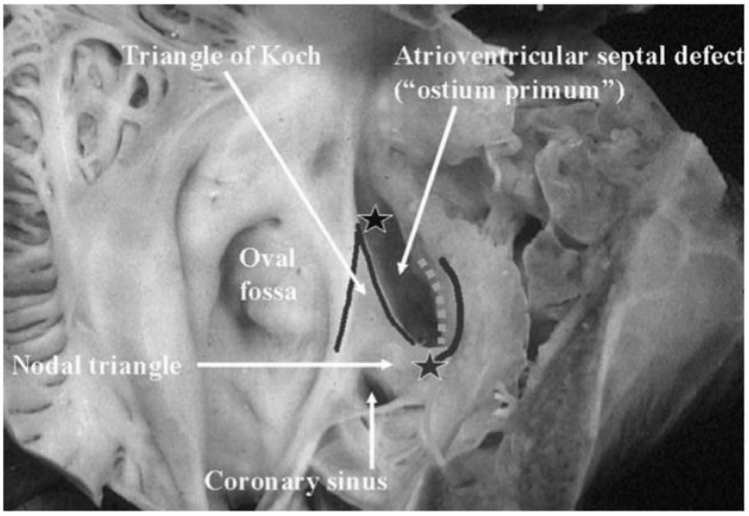



**FIGURE 66-17** The position of the conduction axis in atrioventricular septal defects. The view is from the opened right atrium. The margins of the triangle of Koch are indicated; the superior black star indicates where one would normally expect to find the atrioventricular node (i.e., at the apex of the triangle). However, in this defect, the node has been displaced to the area between the coronary sinus and the crux of the heart (inferior black star). From here, the conduction axis runs along the proximal part of the ventricular crest (dotted line).

## CLINICAL FEATURES

Aside from synchronous congenital malformations, the presentation and clinical findings of patients with AVSD are determined by several factors, among which are the level of shunt and the competence of the left AV valve. Both variables may be the cause of acute and severe presentation.

In the presence of isolated atrial shunting and minimal valvar regurgitation, the presentation is often delayed, akin to a defect in the oval fossa. The findings may be made incidentally, or suspicion may be raised by recurrent chest infections or reduced exercise tolerance.

With a common orifice and shunting at both levels, presentation is usually in infancy, with cardiac failure. The child is diaphoretic and short of breath on feeding and fails to thrive. These problems are compounded if there is severe left AV valvar regurgitation. On examination, the child is undernourished, breathless, and tachycardic, with hepatomegaly. There is a hyperactive precordium with a systolic thrill and a pansystolic murmur of variable grade.

## DIAGNOSIS

On CXR, there is variable cardiomegaly, reflected in the cardiothoracic ratio. If the valve is severely regurgitant, the heart is enlarged in the absence of significant shunting. The pulmonary trunk is similarly engorged, with prominence of the pulmonary vascular markings. With persisting pulmonary hypertension, the heart is not as greatly enlarged, but the pulmonary trunk is prominent, with "pruning" of the markings of the vascular tree.

Although superseded by echocardiography,[43] cardiac catheterization is presently reserved for those patients with complex defects where the intracardiac shunt must be calculated and when operability must be determined in the face of raised pulmonary vascular resistance. Information provided includes the anatomy, degree of AV valvar regurgitation, and quantification of the shunt. The diagnostic hallmark is the "gooseneck" appearance of the LVOT in the anteroposterior projection (Fig. 66-18).[22]

### Echocardiography

This has superseded all other modalities as the pre-,[44,45] intra-,[46–48] and postoperative[49] investigation of choice. Doppler interrogation reveals intracardiac shunting, AV valve function, and patency of the LVOT while also determining the pulmonary vascular pressures. It has also, in recent years, been applied for prenatal diagnosis.[50]

There are a number of anatomic hallmarks. On the four-chamber view, the common AV junction causes loss of the normal offsetting of the AV valves (Fig. 66-19, left). Furthermore, the relationship of the leaflets to the crest of the ventricular septum can be appreciated on this view (Fig. 66-19, right). On the long-axis section, the "gooseneck" deformity of the LVOT is also visible; on the short-axis view, the common AV valve annulus is seen (Fig. 66-20). With separate right and left orifices, the trifoliate left AV valve is seen on short-axis with an exclusive orientation of the leaflets.

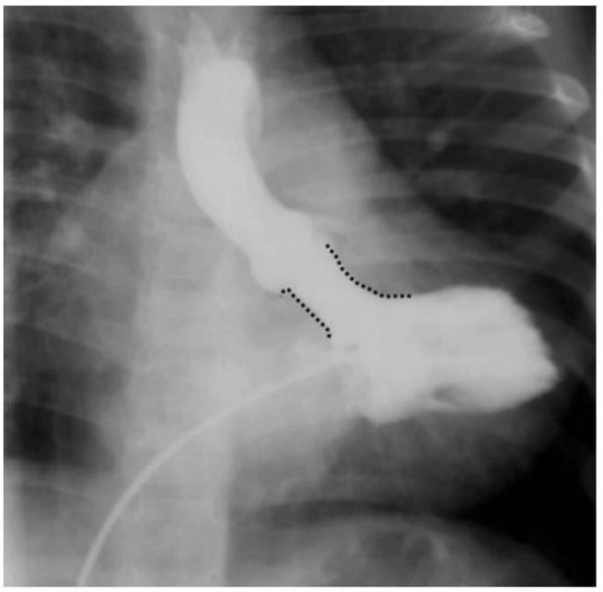


**FIGURE 66-18** An anteroposterior angiocardiographic projection of the heart with an atrioventricular septal defect and common atrioventricular junction. The left ventricular outflow tract is elongated as a "gooseneck" (outlined), since it lies in an unwedged position anterior to the common atrioventricular junction.

The size of the VSD is variable, often being larger beneath the SBL. There will also be variable chordal tethering to its crest. This septal tethering is greatest beneath the IBL, as seen on the four-chamber section. It is therefore important to look for subtle ventricular shunting in the inter-chordal spaces with color-flow Doppler interrogation. Thus, because of this chordal obstruction, the degree of inter-ventricular shunting is greatest with a free-floating SBL.

## NATURAL HISTORY

Without surgical intervention, the natural course will be determined by a number of factors, principally the level and degree of the intracardiac shunting, the pulmonary vascular resistance, and the competence of the left AV valve. It also follows that these factors will affect the timing of surgical intervention and subsequent outcome.

In the absence of significant left AV valvar regurgitation, the natural history of defects with separate orifices will be similar to that of a defect in the oval fossa. Therefore, up to 15 percent of these patients will develop pulmonary hypertension by adulthood, and symptomatic deterioration may coincide with the development of atrial fibrillation.[51]

As predicted, the clinical course of the defect with a common orifice is more pernicious, with early deterioration

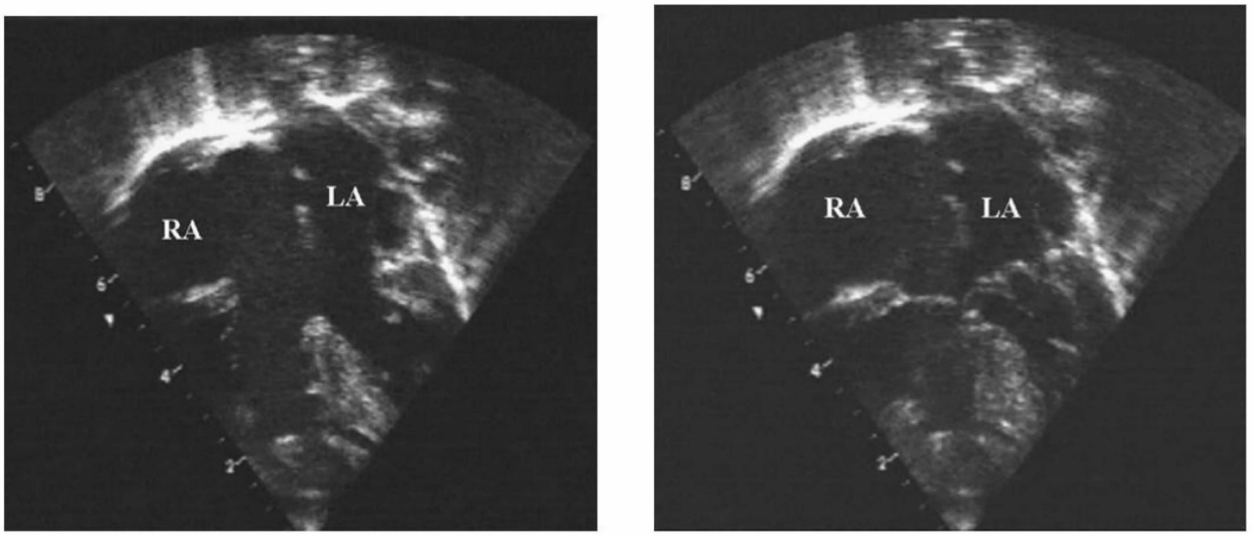



**FIGURE 66-19** Two-dimensional transthoracic echocardiogram of the heart with atrioventricular septal defect in four-chamber view, taken in diastole (left panel) and systole (right panel). Note the tethering of the bridging leaflets to the crest of ventricular septum in systole, as well as the lack of off-setting of the AV valve. LA, left atrium; RA, right atrium.

from pulmonary hypertension, cardiac failure or respiratory infections. It is estimated that up to 80 percent of patients who do not undergo correction die by the age of 2 years.[52]

## SURGICAL MANAGEMENT

Two pivotal events have transformed the surgical repair of AVSDs. The first and most conspicuous was the introduction of cardiopulmonary bypass; this could not have been successful without the other crucial event: mapping of the conduction tissue, by Lev.[53] Up to then, repair was hazardous, even in the best of hands. In 1954, Kirklin and associates successfully closed a defect with separate orifices using the atrial well of Gross. By 1955, defects were being closed under cardiopulmonary bypass using the DeBakey roller pump and wire-mesh screen oxygenator.[54]

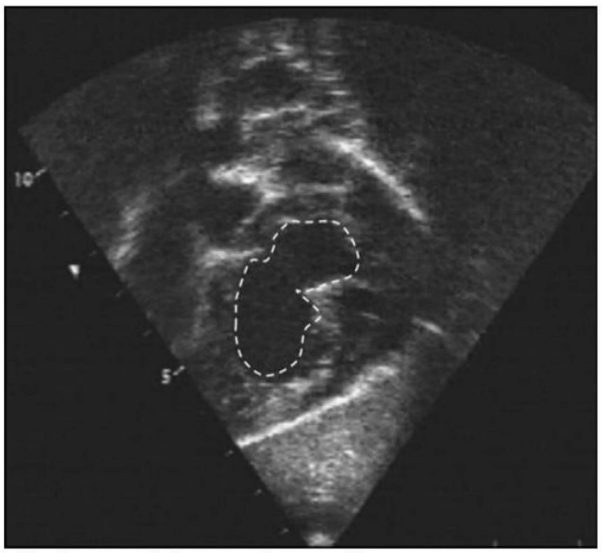


**FIGURE 66-20** The same heart as in Figure 66-18 in short-axis orientation showing the characteristic shape of the common atrioventricular junction (outlined).

Lillehei and associates performed the first repair of the so-called complete defect in 1954 by suturing the inferior rim of the atrial septum directly to the crest of the ventricular septum. Unsurprisingly, this often caused complete heart block, thus worsening valvar regurgitation and subaortic stenosis. It led to the introduction, in 1962,[55] of the single-patch technique as a way of overcoming early mortality. Over the past 4 decades, results have continued to improve, owing to better surgical techniques, more refined bypass circuits, and tailored postoperative care together with the use of permanent pacemaker systems.

### One- Versus Two-Stage Repair

In the modern era, attention has shifted from a two-stage repair [involving initial pulmonary artery (PA) banding - see chapter 62] to complete primary repair in infancy. Two factors have brought about this change of strategy. First, there is greater understanding of the morphology, as mentioned. This also advanced the appreciation of the abnormal pathophysiology. Thus it was recognized quickly that banding was often ineffective in alleviating heart failure in the presence of severe left AV valvar incompetence.[56] Overall, the mortality associated with banding approached 50 percent.[56–58] Within face of these concerns, complete repair before the age

of 2 years was called for, bringing the timing of intervention into line with that of simple VSDs. By the late 1970s, early primary repair had become the norm.[59,60]

Today, initial banding is reserved for complex defects, such as multiple VSDs, concurrent sepsis, and in some cases of the so-called unbalanced AVSDs, when it is possible to delay biventricular repair to a later date.[61,62]

## Timing of Repair

Hand in hand with primary repair is a decline in the age at operation. Independent of age, the timing will also be determined by other factors, such as the pulmonary vascular resistance, size of the intracardiac shunt and the degree of left AV valvar regurgitation. Aside from the protective effects on the pulmonary circulation,[28] earlier age at repair may confer benefits to the competence of the left AV valve. Chronic valvar regurgitation and volume overload lead to progressive annular dilatation with worsening leaflet coaptation. This is accompanied by leaflet dysplasia at the zone of apposition, further affecting the coapting mechanism. This cycle of "regurgitation begets regurgitation" is broken early by timely intervention. As a counterargument to early repair is the possibility of tearing of the sutures at the zone of apposition in patients weighing less than 5 kg at operation.[63]

Until 1973, only six patients below the age of 6 years had undergone attempts to repair defects with a common orifice, with only two survivors. By the late 1990s, the timing had reached the contemporary practice of repair within the first 6 months of life.

With AVSD with separate orifices in the absence of symptoms and left AV valvar regurgitation, repair is performed electively at 3 to 4 years of age, in line with defects in the oval fossa. Surgery is suitably earlier in those presenting with symptoms.

## Principles of Repair

The goals of repair are ventricular septation where there is a common orifice, atrial septation together with repair of the AV valves while avoiding heart block, residual defects, and obstruction of the LVOT. Competence of the left AV valve must be achieved while preventing stenosis of its orifice.

Several techniques have been used to achieve these ends, essentially being variations on the single- or double-patch themes. However, unusual leaflet morphologies add to the complexity.

### APPROACH TO THE HEART, CANNULATION, AND CARDIOPLEGIC ARREST

The technique currently used at Great Ormond Street Hospital is described below. Median sternotomy is used in all cases. After thymectomy, the pericardiotomy is veered slightly to the left of the midline and the pericardium left attached on its right border. The aorta, arterial duct, and caval veins are then mobilized with diathermy. A silk ligature is passed around the arterial duct once this has been identified. In small infants, it may be very delicate, so it is often not ligated until cardiopulmonary bypass is established. This is followed by insertion of 5-0 polypropylene purse-string sutures in the aorta, superior caval vein, and right atrial appendage.

For aortic cannulation, a flexible DLP cannula is used (Medtronic, Grand Rapids, MI). A temporary angled metal Great Ormond Street venous cannula (GU Company, Tricomed, Addiscombe, Surrey, UK) is placed through the right atrial appendage, allowing rapid establishment of cardiopulmonary bypass, followed by ligation of the arterial duct. The superior caval vein is cannulated with a second angled metal cannula appropriate for the caliber of the vessel. Following cannulation of the superior caval vein, the metal cannula is removed from the right atrial appendage and replaced with a vent. The inferior caval vein is then dissected to the first hepatic vein. Once this has been exposed, a 5-0 polypropylene purse-string suture is placed, followed by cannulation. Nylon tape is then used to snare both caval veins.

The patient is cooled to 25°C in the case of the common orifice defect and above 32°C in the defect with separate orifices. The aorta is then cross-clamped and cardioplegia is administered. The right atrium is opened with an incision running parallel to the right AV groove. The left atrium may be vented through either the oval fossa or the right superior pulmonary vein. The latter structure may eventually be used for insertion of a left atrial pressure monitoring line.

### THE DOUBLE-PATCH TECHNIQUE

Irrespective of the patch technique, there are a number of initial stages to be performed prior to septation:

1. **Inspection**: This commences with the position and size of the coronary sinus, proceeding to assessment of the size of the atrial component and patency of the oval fossa. The leaflets of the common AV valve are assessed for accessory orifices. The leaflets are elevated to reveal the ventricular component beneath as well as the state of the subvalvar apparatus. The ventricular septum is also inspected for additional septal defects.
2. **Definition of the "kissing point"** (Fig. 66-21): Bringing together the bridging leaflets over the left side of the ventricular septum allows their natural line of closure to be determined, forming a vital part of valvar repair. Once determined, the kissing point is marked with a 6-0 polypropylene suture.
3. **Closure of the ventricular component** (Fig. 66-22). This is closed with a 0.4-mm polytetrafluoroethylene (Gore-Tex) patch, although other materials may be used. The dimensions of the defect are assessed using silk ties, which are used to fashion out a crescentic patch of Gore-Tex. This is sutured to the right side of the ventricular septum with a continuous 5-0 polypropylene suture. To facilitate

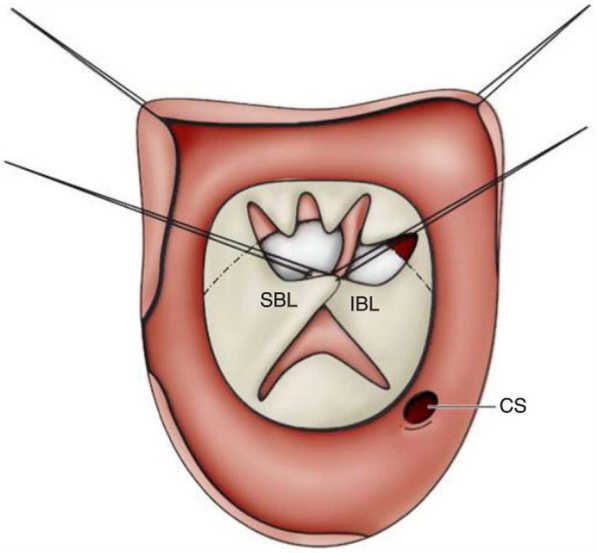



**FIGURE 66-21** Drawing of the surgical repair of the atrioventricular septal defect with a common orifice, using the two-patch technique. The view is in surgical orientation, through the right atrium. The "kissing point" of the superior and inferior bridging leaflets are initially brought together and marked with polypropylene marking sutures. (Modified from Elliott MJ, Jacobs JP. Atrioventricular canal defects. In: Kaiswer LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007. With permission.)

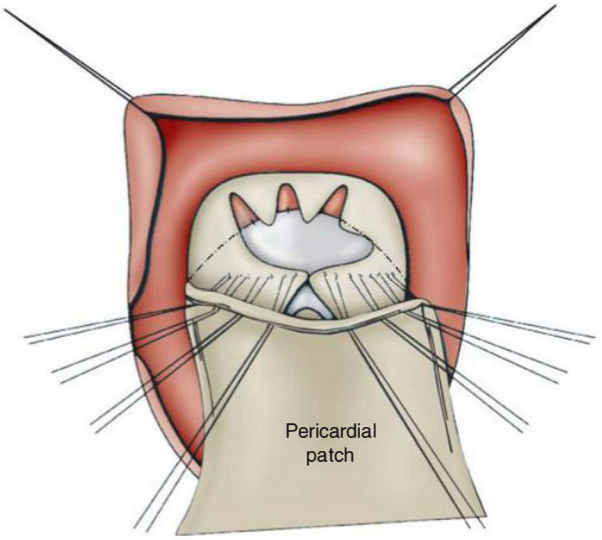



**FIGURE 66-23** Next, the patch of autologous pericardium is secured to the ventricular septal patch and bridging leaflets by a line of double-armed interrupted sutures, released from its pericardial attachment, and slid down into place. (Modified from Elliott MJ, Jacobs JP. Atrioventricular canal defects. In: Kaiswer LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007. With permission.)

this, some small secondary chords may have to be sacrificed. The suture line is commenced close to the annulus through the IBL, where it is well away from the position of the bundle. The first one or two bites are placed with the patch outside the heart. Once fixed, the prosthetic patch is slid into position beneath the bridging leaflets. The suture line then runs deeply along the right side of the septum toward the SBL, weaving through the chords. Finally, it is brought through the SBL, avoiding the aortic valve. A rubber-shod clamp is placed on the free end of the suture.

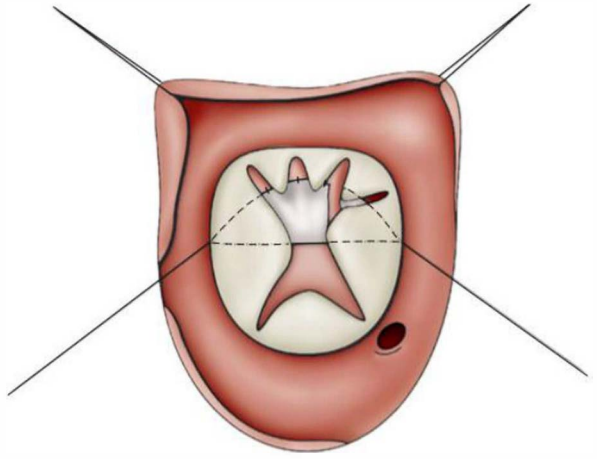


**FIGURE 66-22** The crescentic patch of 0.4-mm Gore-Tex is sutured to the crest of the ventricular septum, keeping the suture line to the right side of the ventricular septum in order to avoid injury to the conduction tissue. (Modified from Elliott MJ, Jacobs JP. Atrioventricular canal defects. In: Kaiswer LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007. With permission.)

4. **Atrial septation** (Fig. 66-23). The atria are septated while separating the common valve into right and left components. Interrupted 6-0 polypropylene sutures, double-armed, are placed along the horizontal margin of the ventricular patch. The sutures are then passed through the bridging leaflets and through the edge of the prepared autologous pericardium. This suture line runs from the inferior to the superior margin of the annulus. Thus, the line passes in an axis that bisects the common junction, its axis defined by the kissing point of the bridging leaflets. The sutures are then tied after the right side of the pericardium has been detached.
5. **Closure of the zone of apposition**. To follow, the bridging leaflets are sandwiched between the two septal patches. Once this has been performed, the pericardial patch is swung over, exposing the newly created left AV orifice. The zone of apposition between the bridging leaflets is closed with one or two interrupted 6-0 polypropylene sutures supported with a small patch of pericardium (Fig. 66-24). The left AV valve is tested with a bulb syringe of cold saline. A commisuroplasty or annuloplasty may improve competence if there is persisting central regurgitation. A Hegar dilator ensures that the repaired valve is not stenotic.

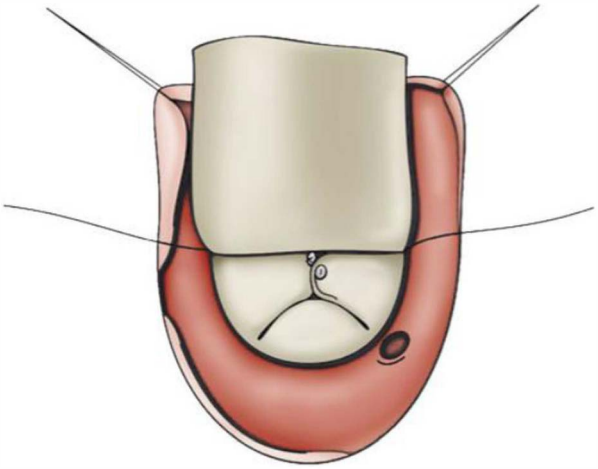


**FIGURE 66-24** Once in place, the pericardial patch is elevated to allow the zone of apposition to be closed with pericardially pledgetted polypropylene sutures. (Modified from Elliott MJ, Jacobs JP. Atrioventricular canal defects. In: Kaiswer LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007. With permission.)

6. The atrial patch is sutured in place with continuous 5-0 polypropylene, avoiding the position of the AV node. The coronary sinus may be left on either side of the patch, but it is committed to the right side in the face of a left superior caval vein. The first suture of the atrial patch is the free end of the ventricular patch suture that was held in a rubber-shod clamp. If the coronary sinus is committed to the right side, the suture line passes around the coronary sinus, close to the eustachian valve of the inferior caval vein, well inferior to the bundle. If the sinus is on the left side, the suture line binds the patch to the left AV valve at the annular margin (Fig. 66-25).

Once the heart is septated, the heart is de-aired and the aortic cross-clamp is removed. Once rewarming is complete, cardiopulmonary bypass is weaned.

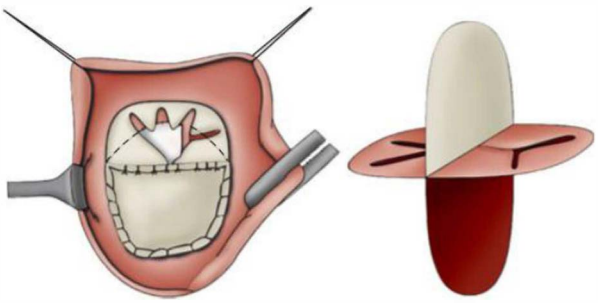


**FIGURE 66-25** The repair is complete when the free edge of the pericardial patch is secured to the leading edge of the atrial septum. In this case, the coronary sinus is committed to the left ventricle. The right-hand panel shows the anterosuperior view of the newly septated heart. (Modified from Elliott MJ, Jacobs JP. Atrioventricular canal defects. In: Kaiswer LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007. With permission.)

## THE SINGLE-PATCH TECHNIQUE

This method has changed little since 1962. In the modern era, a pericardial patch is almost always used to close both ASDs and VSDs. The bridging leaflets are divided in order to accommodate the solitary patch.[64] Given that both bridging leaflets must be anchored to the patch, the suture line is more extensive than with the two-patch technique.

## THE TECHNIQUES COMPARED

Extensive comparisons have been made of the benefits of one technique over the other. The single-patch technique has been hailed as simpler (and therefore superior), with greater exposure of the VSD and subvalvar apparatus[65] and even associated with reduced duration of postoperative ventilator support.[34] However, it has also been criticized for its theoretical effects on valvar competence,[66] since relatively more of the left AV valve is taken up in the suture line, with the risk of dehiscence.[28,67,68] This has caused some to change their technique over time.[28] Furthermore, it has been argued that closure of the zone of apposition may be inappropriate with this technique, since division of the leaflets and resuspension of the valve results in restricted mobility of the SBL.[69] Nevertheless, results are comparable and depend on operator preference.

## THE MODIFIED SINGLE-PATCH TECHNIQUE

This was initially introduced by Rastelli but refined and expanded by Wilcox[70] and the Australian group.[71] Here, the AV valves are sutured directly to the crest of the ventricular septum, simultaneously incorporating a single patch that is anchored to the leaflets and closing the (ASD). Thus, in essence, the defect with the common orifice is converted to one with separate orifices where the valves are bound to the septal crest.

Several centers have adopted it as their standard[76] where it is defended on anatomic principles. Although it is known that the septal scoop is greatest in the setting of a common orifice, this is not the case in 30 to 40 percent of hearts.[19] It follows, therefore, that direct suturing of the leaflets to the septal crest (if the VSD scoop is not of course excessive) is entirely feasible without distortion of the left ventricular outflow or disruption of the natural line of valvar closure. Another argument for this simplified technique is that ventricular septal patches have been getting progressively smaller with time, so that discarding them altogether is the next natural step in the evolution of surgery for AVSD.

## ACHIEVING AND MAINTAINING LEAFLET ATRIOVENTRICULAR VALVAR COMPETENCE

Achievement of a competent left AV valve involves more than closure of the zone of apposition between the bridging leaflets.

Correct sizing of the ventricular patch is the first method, since it supports the annulus. If the patch is too long, the bridging leaflets will fail to coapt. If it is too short, valvar stenosis will ensue.[77]

Despite the observation that the zone of apposition is the most incompetent part of the left AV valve, its closure has not always been advocated. Carpentier[78] has stated that the trifoliate left AV valve is well adapted to its role. Thus, closure of the zone of apposition would reduce valvar opening during diastole and produce undue tension on the suture line.[69,79] Therefore, an integrated trileaflet repair was advocated, based on the native trifoliate appearance.

Nevertheless, others have argued that the zone does not have the characteristic features and support of commissures in the normal AV valves and should therefore be closed.[61]

Some authors have taken the middle ground, repairing only those valves that were incompetent on saline testing[14,80] and not those in the very young because of the risk of tearing the leaflets.[63]

There are certain situations where it is agreed that the zone should be left open to prevent valvar stenosis. One well-recognized situation is that of the solitary left ventricular papillary muscle, or so-called parachute valve. Here, the bridging leaflets have a common papillary muscle insertion, leading to a slit-like valvar orifice. There is a similar risk of stenosis when one is faced with a small left ventricle or in the presence of an accessory left ventricular orifice.[19,81–83] One way of standardizing the decision as to whether or not to close the zone of apposition has called for assessing the size of the left mural leaflet, the angular size of which has been found to be inversely related to the size of the IBL.[19] An angular size of greater than 45 degrees has been used as the determinant of closure.[84]

Commissuroplasty or annuloplasty may also be used to improve competence, either at the commissures or centrally. They have also been used as a "belt and braces" measure in older patients with the defect of separate orifices where there has been chronic annular dilatation.[61,62]

## Atrioventricular Septal Defect with Tetralogy of Fallot

Tetralogy of Fallot is associated with 2.7 to 10 percent of cases of AVSD. Conversely, AVSD is seen in only 1 to 2 percent of cases of ToF.[85] There are a number of issues that must be considered during repair. First is the issue of whether complete primary repair can be carried out at an early stage. Even in the contemporary era, the majority of patients are palliated initially with a systemic-to-pulmonary shunt, the decision being guided by the severity of preoperative cyanosis. However, some have advocated early primary repair, stating that this aggressive strategy negates the risks associated with shunting.[86] However, there is no consensus, so that the age at complete repair varies greatly among different centers, ranging from a few months to several years.

Another issue is the finding that in the combined defect, the SBL is free-floating.[12] This has affected the decision as to whether to use a single- or double-patch strategy.[86,87] Some advocate two-patch repair on the understanding that it reduces the incidence of LVOT obstruction.[88–91] This is because the ventricular septal patch can be easily fashioned into a teardrop shape to accommodate the contour of the deviated outlet septum. Given this and other unresolved issues, such as the impact of both AV and pulmonary valvar dysfunction, mortality is still highly variable, ranging from less than 5 percent[85,88] to 33 percent.[89]

# RESULTS OF REPAIR AND COMPLICATIONS

## Mortality

There has been a striking reduction in the early and late postoperative mortality since the dawn of repair. In the current era, in the situation of a common orifice with no associated defects, balanced ventricles, and in the absence of vascular pulmonary hypertension, the mortality in most reporting centers is less than 5 percent and usually in the order of 1.5 to 3 percent. This is in contrast to 3 decades ago, when mortality was anywhere from 30 to 60 percent. The analysis of these results has also enabled some risk factors to be identified for mortality, some with more consistency than others (Table 66-1).

## Postoperative Complications

Aside from the general risks associated with anesthesia and cardiopulmonary bypass, the following complications are observed with this defect.

**TABLE 66-1: Predictors of Postoperative Mortality in Patients with Complete Atrioventricular Septal Defects**

| Risk Factors for Postoperative | References |
|---|---|
| Preoperative pulmonary hypertension | 35, 88, 89 |
| Preoperative LAVV regurgitation, leaflet dysplasia or dysplastic LAVV | 31, 88, 90–92 |
| Unbalanced ventricles | 15, 90, 93 |
| Double-orifice LAVV or solitary papillary muscle | 28, 31, 64 |
| Additional ventricular septal defects | 31 |
| Early era of operation | 34, 64, 92 |
| Postoperative pulmonary hypertensive crisis | 28 |
| Postoperative LAVV regurgitation | 28, 64 |
| Young age at repair | 29 (before 1976), 92 (before 1990), 89 |
| Low body weight | 35, 89, 90 |
| Long aortic cross-clamp time | 35, 89 |
| Requirement for preoperative inotropic support | 88 |
| Requirement for preoperative ventilatory support | 94 |
| Nonclosure of the zone of apposition | 89, 95 |
| Coarctation of the aorta | 92 |

LAVV, left atrioventricular valve.

### PULMONARY HYPERTENSIVE CRISIS

The incidence of this complication has fallen with the advent of reduced age at primary repair, but the risk is still significant in older patients, those with preoperative pulmonary hypertension, and those with moderate-to-severe preoperative left AV valvar regurgitation. In these cases, concurrent use of both pulmonary artery and left atrial pressure lines is invaluable in the first 24 to 36 h after surgery. Scenarios that may trigger a crisis—such as acidosis, hypoxia, or agitation—must be avoided (see Chapter 60). Thus, older patients are intubated and sedated for longer periods in the postoperative phase. α-Adrenergic blockers, such as phenoxybenzamine, may be used prophylactically, preoperatively, and during rewarming. During a crisis, the patient is sedated and hyperventilated, so that the $Paco_2$ falls to below 3.5 kPa. Paralysis may also be instituted, together with intravenous nitroprusside or inhaled nitric oxide.

### HEART BLOCK

In the modern era, when the position of the conduction bundle has been defined, the prevalence of this complication has fallen to 1 to 2 percent. The key is careful suture placement in the region of the coronary sinus, remembering that the conduction system runs the same course irrespective of the number of orifices. Following operation, in the case of temporary heart block that may occur in the context of regional conduction tissue edema, the patient should leave the operating room with temporary pacing wires.

### LEFT ATRIOVENTRICULAR VALVAR REGURGITATION

This may be considered as an early or late postoperative complication that might require reoperation. It may be recognized as a persistently elevated left atrial pressure and failure to wean from intubation, being confirmed by echocardiography. Early reoperation for regurgitation has been consistently reported in 5 to 7 percent of patients, with little change over the years.[15,64,100] It may be associated with technical factors, such as closing the zone of apposition; but in some series the use of closure of the zone with annuloplasty did not affect the overall incidence of regurgitation.[64] Some have also suggested that the severity of preoperative regurgitation correlated with the degree of postoperative insufficiency,[28] whereas others have found no relationship between the two.[32]

Late regurgitation, measured as freedom from reoperation, ranging from about 80 to 90 percent at 10 years.[93,96,99] The incidence of this complication has similarly shown little change over the years, being more common in such situations as in the setting of a double-orifice valve, nonclosure of the zone of apposition, non-Down patients,[94,100] and a dysplastic left AV valve. Recently, division of the SBL at operation during patch placement has also been associated with an increased incidence of long-term left AV valve regurgitation.[101] Table 66-2 summarizes the risk factors identified in the literature for early and late AV valvar regurgitation.

**TABLE 66-2: Predictors of Postoperative Left Atrioventricular Valve (LAVV) Regurgitation in Patients with Complete Atrioventricular Septal Defects**

| Risk Factors for Postoperative Left Atrioventricular Valvar Regurgitation | References |
|---|---|
| Preoperative LAVVR | 96–98 |
| Nonclosure of the zone of apposition | 61, 90, 96, 99 |
| Non-Down AVSD | 38, 90 |
| Leaflet dysplasia | 100 |
| Double-orifice left atrioventricular valve | 96, 97, 99, 100 |
| Solitary papillary muscle arrangement | 97 |
| Older age at operation | 38 |
| Division of the bridging leaflets at operation | 97 |
| Earlier era of operation | 95 |
| Unbalanced | 90, 100 |
| atrioventricular septal defects | — |
| Preoperative pulmonary hypertension | 100 |

## THE FUTURE

Although, in terms of both mortality and morbidity, surgical repair of this defect has come a very long way, the main issue for the future involves long-term durability of the repair and quality of life. With this in mind, the stagnant incidence of long-term left AV valvar deterioration will be tackled successfully only by thoroughly understanding the form and function of the valve, with all of its morphologic nuances.

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## ATRIOVENTRICULAR SEPTAL DEFECTS BOARD REVIEW QUESTIONS (CHAPTER 66)

1. Which is correct regarding anatomy and morphology of AVSD?
   A. The hinges of the mitral valve are anchored by muscle throughout the right AV junction.
   B. The disparity between the muscular AV junction and the valvar annulus is most clearly seen at the tricuspid valve.
   C. The mitral annulus lies at a more apical position than the tricuspid annulus.

D. The AV septum refers to the AV component of the fibrous membranous septum.
E. The common AV junction is not seen in the absence of septal deficiency.

2. Which is true regarding leaflet arrangement and subvalvar apparatus in AVSD?
   A. The SBL is analogous to the tricuspid anterior leaflet.
   B. The IBL is analogous to the mitral anterior leaflet.
   C. The left-sided papillary muscles are located in the same vertical plane.
   D. The degree of bridging of the IBL across the VSD is the basis of the Rastelli classification.
   E. The Rastelli type C defect has the greatest prevalence.

3. Which is correct regarding morphology of AVSD?
   A. The pattern of blood flow between the chambers is largely determined by chordal and leaflet anatomy.
   B. The degree of ventricular septal "scooping" is less extensive in hearts with a common orifice.
   C. The connecting leaflet "tongue" over the ventricular septal crest is a continuation of the common annulus.
   D. Obstruction of the subaortic outflow tract is common.
   E. The nodal triangle is displaced anteriorly and superiorly.

4. Which is correct regarding surgical technique for repair of AVSD?
   A. The VSD patch is sutured to the left side of the ventricular septum.
   B. Secondary chordae may need to be sacrificed during VSD closure.
   C. The atria are septated before separating the common valve orifice.
   D. Annuloplasty is not useful if there is persisting central regurgitation.
   E. The coronary sinus should be placed on the left side in the setting of a left superior caval vein.

5. Which of the following is true for results of surgical repair of AVSD?
   A. Operative mortality is 5 to 10 percent.
   B. Pulmonary hypertensive crisis is more common in younger patients.
   C. Heart block occurs in 3 to 5 percent.
   D. Closing the zone of apposition is associated with early reoperation for insufficiency.
   E. Late regurgitation is more common in patients with Down syndrome.

## ANSWERS

1. **Answer: D.** The AV septum is a term that is reserved for the AV component of the fibrous membranous septum. The hinges of the tricuspid valve are anchored by muscle throughout the right AV junction. The disparity between the muscular AV junction and the valvar annulus is most clearly seen at the mitral valve. The tricuspid annulus lies at a more apical position than the tricuspid annulus. The common AV junction is the fundamental feature of AVSD and is seen even in the absence of septal deficiency.
2. **Answer: C.** The left-sided papillary muscles are located in the same vertical plane. The SBL and the IBL have no counterparts to the normally septated heart. The degree of bridging of the SBL across the VSD forms the basis of the Rastelli classification. The Rastelli type A defect is the most common, occurring in 50 to 75 percent of cases.
3. **Answer: A.** The pattern of blood flow between the chambers is largely determined by chordal and leaflet anatomy. The degree of ventricular septal "scooping" is more extensive in hearts with a common orifice. The connecting leaflet "tongue" over the ventricular septal crest is not a continuation of the common annulus and has a variable extent. Obstruction of the subaortic outflow tract is uncommon. The nodal triangle is displaced posteriorly and inferiorly.
4. **Answer: B.** Small secondary chordae may need to be sacrificed to facilitate VSD closure. The VSD patch is sutured to the right side of the ventricular septum. The atria are septated during at the same time the common valve is separated into right and left components. Annuloplasty or commissuroplasty are useful if there is persisting central regurgitation. The coronary sinus should be committed to the right side in the setting of a left superior caval vein.
5. **Answer: D.** Closing the zone of apposition has been associated with early reoperation for insufficiency. Current operative mortality is less than 5 percent. Pulmonary hypertensive crisis is more common in older patients, existing preoperative pulmonary hypertension, and in patients with moderate or severe left AV valve regurgitation. Postoperative heart block occurs in 1 to 2 percent of patients. Late regurgitation is more common in patients with a double-orifice valve, nonclosure of the zone of apposition, those without Down syndrome, and a dysplastic left AV valve.

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# 67 Aortopulmonary Window

*Victor O. Morell*
*Ergin Kocyildirim*

**KEY CONCEPTS**

- Epidemiology
  - Aortopulmonary (AP) window is a rare congenital anomaly, representing 0.2 to 0.5 percent of all cases of congenital heart disease.
- Pathophysiology
  - An abnormal communication between the ascending aorta and main or branch pulmonary artery results in severe left-to-right shunting. The degree of pulmonary overcirculation, pulmonary hypertensive vascular changes, congestive heart failure, and failure to thrive depend on associated anomalies and the size of the defect, which is often large enough to allow equalization of pulmonary and aortic pressures. Associated malformations are present in 50 to 60 percent of cases and include interrupted aortic arch, tetralogy of Fallot and anomalous origin of the right pulmonary or coronary artery.
- Diagnosis
  - Two-dimensional echocardiography provides accurate identification and localization of AP window as well as definition of associated lesions.
- Treatment
  - Surgical closure of large defects is indicated at the time of diagnosis in order to avoid early development of fixed pulmonary hypertension. Patch repair using a transaortic, transpulmonary, or "sandwich" approach has excellent outcomes. Small defects can be ligated or approached by percutaneous techniques.
- Outcomes/prognosis
  - Operative mortality is reported at less than 10 percent, with long-term prognosis largely dependent on the development of pulmonary hypertensive changes.

## INTRODUCTION

Aortopulmonary (AP) window is a rare congenital anomaly, accounting for 0.2 to 0.5 percent of all congenital heart defects.[1] It consists of a communication between the aorta and the pulmonary artery or its branches. Although closely related to AP window, pulmonary artery origin from the ascending aorta (also erroneously termed "hemitruncus") is classified as a separate defect.

AP window was first described by Elliotson in 1830 in an autopsy study.[2] In 1948, Robert Gross successfully ligated an AP window in a patient undergoing a thoracotomy for closure of a patent ductus arteriosus (PDA).[3] In 1957, Cooley and associates described the first successful repair of AP window using cardiopulmonary bypass.[4]

## PATHOPHYSIOLOGY

The pathophysiology of AP window is similar to that of a ventricular septal defect, PDA, or truncus arteriosus consisting of a left-to-right shunt. The amount of left-to-right shunting is related to the size of the defect and the pulmonary vascular resistance. Patients with small defects can be completely asymptomatic. With large defects, and as the pulmonary vascular resistance decreases in the first weeks of life, symptoms of congestive heart failure develop rapidly, and irreversible pulmonary vascular disease can occur as early as during the first 12 months of life. If untreated, 40 percent of patients will die of intractable heart failure during the first year of life, and survivors will succumb to the sequelae of congestive heart failure and severe irreversible pulmonary vascular disease during childhood (Fig. 67-1).[5]

## EMBRYOLOGY AND MORPHOLOGY

This defect has also been called AP septal defect; however, in terms of the structure of the postnatal heart and beyond the initial few months of gestation, there is no such thing as an AP septum. Almost as soon as the aortic and pulmonary pathways become separate entities within the developing heart, each of the intrapericardial arterial trunks develops its

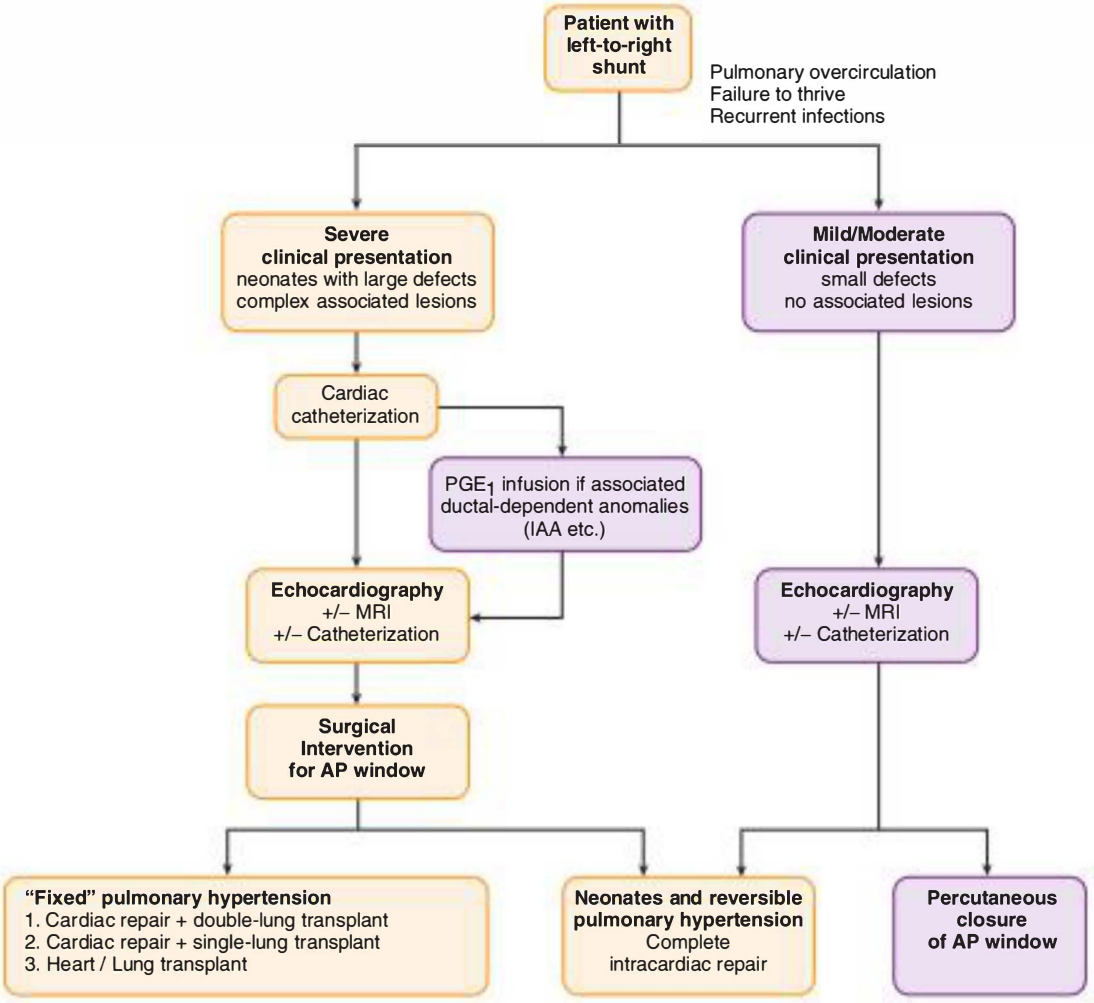



**FIGURE 67-1** Decision-making flowchart.

own discrete arterial wall. AP window is the failure of formation of the separate adjacent walls of the intrapericardial arterial trunks, with persistence of the AP foramen that certainly does exist during embryological development.[6] This defect can be differentiated from common arterial trunk by the presence of two separate arterial valves arising from separate subarterial ventricular outflow tracts.

AP window was classified by Mori et al.[7] into three types (Fig. 67-2):

- *Type I*: The most common type; involves proximal defects located between the semilunar valves and the pulmonary bifurcation.
- *Type II*: Distal defects located in the uppermost portion of the ascending aorta, with the posterior border of the defect formed by the pulmonary bifurcation.
- *Type III*: The defect is posterior in the aorta, creating a communication with the right pulmonary artery.

The Congenital Heart Surgery Nomenclature and Database project uses a classification system that is similar to the one just described.[8] A *Type 1 proximal defect* involves an AP window located just above the sinus of Valsalva, a few millimeters above the semilunar valves, with a superior rim but little inferior rim separating the AP window from the semilunar valves. *Type 2 distal defect* is located in the uppermost portion of the ascending aorta, with a well-formed inferior rim but little superior rim. *Type 3 total defect* involves the majority of the ascending aorta, with little superior and inferior rims. The *intermediate type* is a defect similar to the Type 3 but with well-defined superior and inferior rims. Interrupted aortic arch (IAA) is one of the most common associated cardiovascular lesions seen in patients with an AP window; the ventricular septum is usually intact and type A interruption is most commonly encountered.

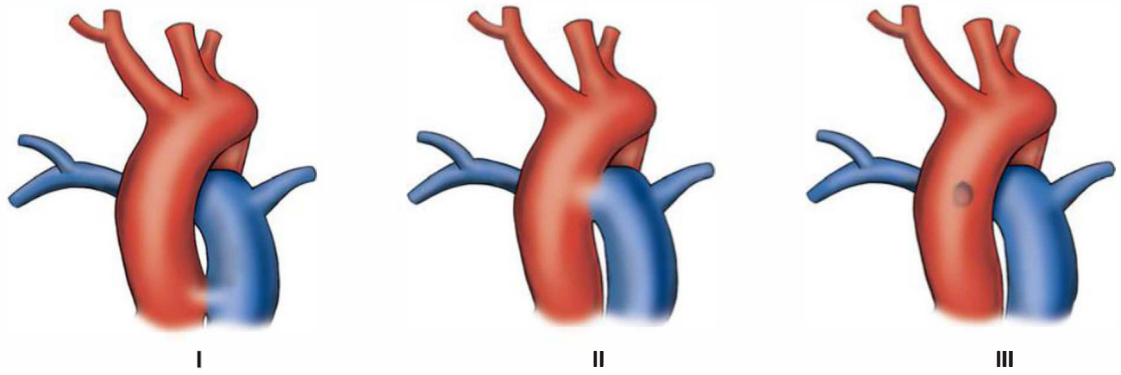



**FIGURE 67-2** Mori's classification of AP window.

AP window is also associated with VACTERL syndrome, which involves vertebral anal, tracheoesophageal renal and limb anomalies. Other associated lesions include tetralogy of Fallot, ventricular and atrioventricular septal defects, anomalous origin of the either coronary arteries from the pulmonary artery, transposition of the great arteries, and double aortic arch.

## CLINICAL FEATURES

The clinical presentation is related to the magnitude of the left-to-right shunt. In early life patients present with signs and symptoms of congestive heart failure, including failure to thrive and frequent respiratory tract infections. The smaller size defects are associated with minimal or no symptoms. On cardiac ausculation a systolic murmur is usually heard. Cyanosis is a late finding, presenting with the development of severe pulmonary vascular obstructive disease. When associated malformations are present, the clinical presentation can change to reflect the combined hemodynamic features, with IAA usually presenting with metabolic acidosis and poor perfusion after PDA closure, making the clinical diagnosis of AP window more challenging.

## DIAGNOSIS AND IMAGING

Depending on the magnitude of the shunt, chest x-ray commonly shows cardiomegaly with increased pulmonary vasculature markings. Electrocardiography may show biventricular hypertrophy. Echocardiography can demonstrate the defect, as well as most associated cardiac malformations, in the majority of the patients. Cardiac catheterization is usually not needed, unless significant associated defects are present that cannot be reliably assessed by echocardiography and other noninvasive imaging methods such as cardiac computed tomography (CT) or magnetic resonance imaging.

## SURGICAL MANAGEMENT AND OUTCOMES

The author's approach usually involves surgical repair as soon as the lesion is diagnosed. These patients will typically have significant left-to-right shunting and demonstrate signs of rapid diastolic aortic runoff. The key aspect of preoperative management is optimization of the $Q_p/Q_s$ in order to avoid low systemic blood flow (Chapter 60). Given the excellent surgical results in young infants (especially in the absence of associated lesions) delaying surgery in clinically symptomatic patients is usually not indicated even in low-birth-weight infants and neonates.

Since the first successful repair by Gross over 5 decades ago, a variety of different techniques have been reported. The currently preferred surgical approach involves repair via a median sternotomy with the use of cardiopulmonary bypass with mild or moderate hypothermia. Both branch pulmonary arteries need to be controlled with tourniquets as soon as cardiopulmonary bypass is established in order to prevent excessive pulmonary runoff. Under cardioplegic arrest the AP window is entered by a vertical incision and occluded (septated) with a patch (Fig. 67-3). Another option is to completely divide the AP window, separating the aorta from the pulmonary artery and repairing both great vessels with separate patches, or to perform an aortotomy and repairing the window through the aorta. This is particularly useful in case of communication between the aorta and the right branch pulmonary artery. Some cases of percutaneous closure have been reported with favorable results in specific situations, such as a small (3–4 mm) defect without any associated lesions.[9,10] In the early postoperative phase, hemodynamic management focused on the prevention of pulmonary hypertensive crisis is crucial, especially in patients in whom the defect is diagnosed late.

The operative morbidity and mortality rates for repair of an isolated AP window are very low.[11–14] The late results are also excellent, with an actuarial survival rate reported between 70 to 90 percent at 10 years. The outcome of

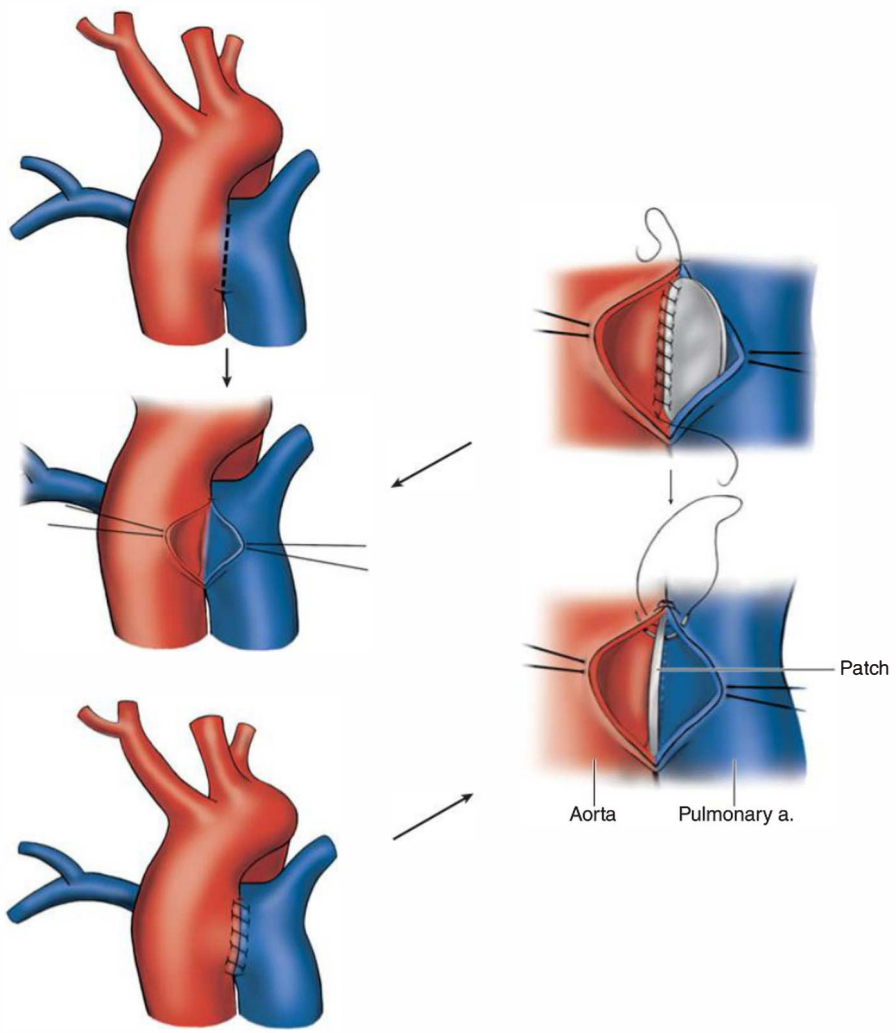



**FIGURE 67-3** Repair of AP window with a prosthetic patch. The anterior wall of the "window" is opened and the patch is sewn to the edges of the defect.

patients with significant associated malformations is determined primarily by the severity of associated lesions rather than by the mere concomitant diagnosis of AP window. The simultaneous presence of IAA (Chapter 79) has been found to be an independent risk factor for mortality.[11] The adverse outcomes in this particular group of patients, including reintervention and mortality, are directly related to the arch repair.[15]

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## AORTOPULMONARY WINDOW BOARD REVIEW QUESTIONS (CHAPTER 67)

1. Which is true regarding pathophysiology of AP window?
   A. It is similar to truncus arteriosus with a right-to-left shunt.
   B. Small defects may be asymptomatic.
   C. Large defects become symptomatic as pulmonary vascular resistance increases.
   D. Irreversible pulmonary vascular disease can occur as early as 3 months of life.
   E. Untreated, 80 percent of patients will die within the first year.

2. Which is correct regarding classification of AP window according to the Congenital Heart Surgery Nomenclature and Database project?
   A. Type 3 defect = located just above the sinus rim
   B. Type 1 defect = located at uppermost portion of ascending aorta
   C. Type 2 defect = majority of ascending aorta
   D. Intermediate defect = similar to type 1 defect with well-defined rims
   E. Type A IAA is a common association.

3. Which is not associated with AP window?
   A. VACTERL syndrome
   B. Tetralogy of Fallot
   C. Atrioventricular septal defect
   D. Hypoplastic left heart syndrome
   E. Double aortic arch

4. Which of the following is correct regarding surgical repair of AP window?
   A. Deep hypothermic circulatory arrest is the preferred approach.
   B. Branch pulmonary arteries are not mobilized to prevent distortion.
   C. The window is repaired through the pulmonary artery.
   D. Percutaneous closure can be performed for small defects.
   E. Postoperative pulmonary hypertensive crisis is unusual.

5. Which is true regarding outcomes after repair of AP window?
   A. Operative mortality rates are 10 to 15 percent.
   B. Late survival is 50 percent at 10 years.
   C. Outcome is primarily determined by the severity of the defect.
   D. Presence of concomitant interrupted arch is an independent risk factor for mortality.
   E. Adverse outcomes are not related to concomitant repair of an interrupted arch.

## ANSWERS

1. **Answer: B.** Small defects may be entirely asymptomatic. The shunting is left-to-right, similar to truncus arteriosus. Large defects become symptomatic as pulmonary resistance falls, and irreversible pulmonary vascular disease occurs as early as 1 year of age. Untreated, 40 percent of patients will die within the first year.
2. **Answer: E.** Type A IAA is a common association. A type 1 defect is located at just above the sinus rim, a type 2 defect is at the uppermost portion of the ascending aorta, and a type 3 defect is the majority of the ascending aorta. An intermediate defect is similar to a type 3 defect and has well-defined rims.
3. **Answer: D.** Hypoplastic left heart syndrome is not associated with AP window. The remaining conditions are associated with this defect.
4. **Answer: D.** Defects less than 3 to 4 mm and without associated anomalies can be successfully closed with a percutaneous approach. Deep hypothermic circulatory arrest is not usually necessary, and the branch pulmonary arteries are mobilized and controlled to prevent excessive runoff. The window is repaired through the aorta. Postoperative pulmonary hypertensive crisis is common, especially in patients with a delayed diagnosis.
5. **Answer: D.** Presence of concomitant interrupted arch is an independent risk factor for mortality, and adverse outcomes in these patients are directly related to the arch repair. Late outcomes are primarily determined by associated anomalies rather than the specific type of AP window. Operative mortality rates are low and late survival is 70 to 90 percent at 10 years.

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# 68

# Tetralogy of Fallot

*Osami Honjo*
*Glen S. Van Arsdell*

## KEY CONCEPTS

- Epidemiology
  - The prevalence of tetralogy of Fallot (TOF) is 0.21 to 0.36 per 1000 live births, accounting for approximately 7 to 10 percent of all congenital heart disease (CHD). 22q11 deletion is seen up to 20 percent of patients with TOF.
- Morphology
  - The essence of TOF anatomy is the anterocephalad deviation of the muscular outlet septum, which causes right ventricular outflow tract (RVOT) obstruction, override of the aorta, and malaligned ventricular septal defect (VSD). As a result of RVOT obstruction (RVOTO), the patients with TOF have various degree of right ventricular (RV) hypertrophy. The pulmonary valve (PV) is commonly bicuspid and has variable hypoplasia and dysplasia. TOF hearts commonly have multi-level obstruction: at infundibulum, PV, main and branch pulmonary arteries (PAs). Coronary artery anamalies occur in up to 5 percent of patients with TOF.
- Pathophysiology
  - The pathophysiology of TOF largely depends on the degree of RVOTO: mild RVOTO results in a predominant left-to-right shunt ("pink" TOF), whereas severe RVOTO results in right-to-left shunt and cyanosis. Some neonates with severe RVOTO are dependent on the presence of a patent ductus arteriosus (PDA) for pulmonary perfusion.
- Clinical features
  - Patients with very mild RVOTO have symptoms of congestive heart failure due to the left-to-right shunt. Those with moderate or severe RVOTO have various degree of cyanosis, that can be episodic (cyanotic spells). In the extreme form of RVOTO, neonates with duct-dependent pulmonary circulation become profoundly cyanotic as the PDA closes.
- Diagnosis
  - Typically, CXR shows decreased pulmonary vascular markings, upturned apex of the heart, and a pulmonary concavity at the upper left heart border, forming a "boot-shaped heart." Electrocardiogram shows rightward QRS axis and various degree of RV hypertrophy. Echocardiography is the most important diagnostic modality for delineating anatomy, including nature and degree of RVOTO, aortic override, type of VSD, PV and PAs. Cardiac catheterization, computed tomography (CT), and magnetic resonance imaging (MRI) can be useful in selected cases with unclear anatomy.
- Treatment
  - Prostaglandin $E_1$ ($PGE_1$) infusion is administered in patients with severe RVOTO and duct-dependent pulmonary circulation. Indication for surgery in the presence of the lesion. Symptomatic neonates are treated with early repair or stenting of RVOT. Patients with no or mild-to-moderate cyanosis typically undergo surgery at 4 to 6 months of age, or when cyanosis gets progressive. In the current era, primary repair is a preferred approach over palliation, with focus on preserving the PV annulus.
- Outcomes
  - Outcomes are excellent, with operative mortality below 3 percent in contemporary series. One-third of patients require late reintervention for residual RVOTO or VSD, and PV implantation. Late survival is 85 to 87 percent at 30 years after repair.

## INTRODUCTION

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease (CHD). The anatomical essence of TOF is the anterocephalad deviation of the infundibular septum, which causes various degree of right ventricular outflow tract (RVOT) obstruction and subsequent right ventricular (RV) hypertrophy.[1–3] The malalignment of the infundibular septum results in a biventricular connection of the aortic valve, i.e., aortic override, and a subaortic ventricular septal defect (VSD) (Fig. 68-1). Although the characteristics of the intracardiac anomalies are predominantly determined by the anterocephalad deviation of the infundibular septum,[3] the subsequent degree of RVOT obstruction (RVOTO) varies significantly, yielding a wide spectrum of anatomy and physiology within the entity. The reported natural history of untreated tetralogy discloses survival rates of approximately 75 percent and 30 percent at 1 and 10 years of age, respectively.[4] The major causes of death in patients with unrepaired TOF include severe hypoxia (62 percent) and cerebrovascular events (30 percent).[5] Surgical strategies for management have evolved from staged repair with an initial systemic-to-pulmonary shunt and subsequent late repair to primary intracardiac repair in early infancy. Clinical outcomes have dramatically improved along with the evolution of surgical strategy.[6] In this chapter, clinical presentation, diagnosis, and current therapeutic strategies for TOF with pulmonary stenosis are discussed. TOF with pulmonary atresia is discussed in Chapter 69. Two important subgroups, namely TOF with absent pulmonary valve (PV) and TOF with atrioventricular septal defect (AVSD) are discussed in the latter part of this chapter.

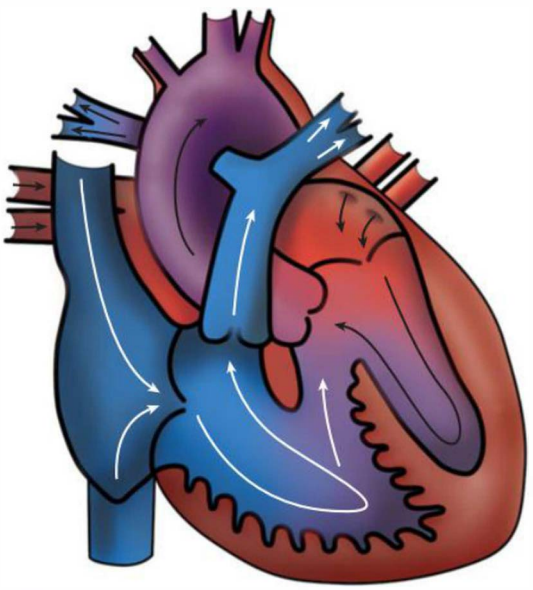


**FIGURE 68-1** Diagram of typical tetralogy of Fallot. The presence of right ventricular outflow tract obstruction and VSD allows right-to-left shunting at the ventricular level.

## EPIDEMIOLOGY AND ETIOLOGY

The prevalence of TOF is 0.21 to 0.36 per 1000 live births as reported in the Baltimore-Washington Infant Study and other large cohort studies,[7,8] accounting for approximately 7 to 10 percent of all forms of CHD. The exact etiology is largely unknown. Most cases are sporadic, although rare familial cases with a missense mutation in JAG1 (jagged 1 gene) have been reported.[9] The risk of recurrence in siblings is approximately 1 to 3 percent.[10,11] Microdeletion of chromosome 22q11 is strongly related to some forms of CHD including TOF. 22q11 deletion is seen in 12 to 20 percent of the patients with TOF.[12]

## ANATOMY

The unifying anatomic feature for TOF is the anterocephalad deviation of the muscular outlet septum relative to the limbs of the septomarginal trabeculation. The subpulmonary stenosis is caused by the deviated outlet septum combined by the hypertrophied septoparietal trabeculations and results in a "squeeze" effect. Anterocephalad deviation of the outlet septum can also be seen in the absence of significant subpulmonary stenosis. This clinical condition is also known as "pink" tetralogy and the septal defect as an "Eisenmenger VSD."[13] The infundibulum is generally longer than that of normal hearts,[14] although there is a significant variability in infundibular length. The infundibulum can also be completely absent.[2] Additional subpulmonary stenosis can be caused by a hypertrophied moderator band or infundibular trabeculations. RV hypertrophy is generally mild at birth, and becomes prominent over time.

As a result of the deviated infundibular septum, the aorta is shifted anteriorly toward the RV, thus overriding the interventricular septum. The degree of aortic override varies from 15 to 95 percent.[2] If there is more than 50 percent override of the aorta, the lesion is referred to as tetralogy-type double outlet RV (Chapter 71).[15] The anatomical features of those hearts are essentially the same as those observed in typical tetralogy.

The VSD in tetralogy is located just beneath the overriding aorta and is usually large and unrestrictive. It can rarely be restricted by tricuspid valve tissue or septal hypertrophy.[16] The majority of VSDs are perimembranous (80 percent), but they can occasionally be subarterial or doubly committed.[2] In a typical TOF VSD, the defect is cradled by the anterior–superior rim (that inserts to the deviated outlet septum) and the posterior–inferior rim of the septomarginal trabeculation. The anterior–superior margin of the defect is the muscular outlet septum and the ventriculo-infundibular fold (the roof of the outlet septum). The inferior–posterior margin of

the defect is muscular. Separating these two limbs is an area of fibrous continuity between aortic and tricuspid valve leaflets, which incorporates the remnant of perimembranous septum (membranous flap). The VSD can also be called a conal septal malalignment defect, and differs from the typical perimembranous defect in that it is rare for chords of tricuspid valve to attach to the margins. The atrioventricular (AV) conduction axis is located around the apex of the triangle of Koch and penetrates the central fibrous body in the area of the remnant of the perimembranous septum. Approximately one-fifth of tetralogy patients have a muscular margin along the entire perimeter of the VSD, a feature most frequently seen in the Asian population.[17] In this defect, the posterior–inferior rim of the septomarginal trabeculation inserts on the outlet septum and the perimembranous region is entirely intact. The rarest type of VSD is the doubly committed juxta-arterial defect, which is more common among patients from the Far East, South America, and Mexico. Unlike the vast majority of the VSDs in tetralogy, this form of tetralogy is characterized by the fact that the anterior–superior rim of the defect is a fibrous raphe between the leaflets of the aortic and PVs. The muscular outlet septum is deficient.

The PV in patients with TOF is most commonly bicuspid and characterized by a small annulus and thickened, dysplastic leaflets. There can occasionally be a tricuspid arrangement of the leaflets but they are usually small and dysplastic as well. PV leaflets are sometimes absent, and this is frequently associated with markedly dilated main pulmonary artery (PA) and its branches, resulting in a completely different physiology (absent PV syndrome).[18] Stenosis is also common in the left PA, main PA, and the branch PA bifurcation.[19] The left PA often originates more distally from the main PA and takes off with an abnormal acute angle, which may result in left PA stenosis. The left PA can be isolated and supplied by an arterial duct (discontinuous branch pulmonary arteries). Major aortopulmonary collateral arteries (MAPCAs) can coexist but are more common in the setting of TOF and pulmonary atresia (see Chapter 69).

A patent oval foramen or atrial septal defect is the most commonly associated lesion seen in patients with tetralogy (also known as pentalogy of Fallot). Other associated lesions include additional muscular VSDs, straddling of the tricuspid valve, common AV valve (TOF with AVSD), and right aortic arch. It is not uncommon to have coronary artery anomalies, including anomalous origin of the anterior descending coronary artery from the right coronary artery (2–3 percent), the presence of an accessory left anterior descending artery from the right coronary artery (5–6 percent), and a single coronary artery.[20] These coronary artery abnormalities may have surgical implications in terms of RVOT reconstruction.

## PATHOPHYSIOLOGY

The pathophysiology of TOF largely depends on the particular anatomical features and, most importantly, on the degree of RVOTO. Neonates or infants with TOF who do not have established RVOTO may have a moderate to large left-to-right shunt through the large VSD. The physiology in this situation is similar to that of an isolated VSD with pulmonary overcirculation. As RVOT muscle obstruction develops over time, the direction of the shunt at the VSD level may become bidirectional. In neonates with severe RVOTO, the direction of the shunt across the VSD can be exclusively or predominantly from right to left. For severe forms of TOF, pulmonary blood flow can be entirely duct-dependent.

The direction of the shunt at the atrial level is typically from left to right or bidirectional. The shunt can be bidirectional or predominantly from right to left if pulmonary vascular resistance is still high in the neonatal period, or if the RV has reduced compliance due to progressive RV hypertrophy.

## DIAGNOSIS

### Clinical Presentation

Neonates with severe RVOTO may present with significant persistent cyanosis at birth. Profound cyanosis may result in metabolic acidosis, compensatory tachypnea, and respiratory alkalosis. Pulmonary perfusion is, in this context, often duct-dependent. If the arterial duct is widely open, patients may not disclose intense cyanosis in spite of the presence of RVOTO. Infants with moderate RVOTO may present with cyanosis in the first few weeks of life with a systolic murmur. Development of cyanosis is usually correlated with the development of infundibular stenosis and RV hypertrophy. Infants with mild or minimal RVOTO may present with nonspecific symptoms of congestive heart failure because of a large left-to-right shunt. Possible symptoms include feeding, poor weight gain and tachypnea. There is generally no cyanosis but may become prominent as RVOTO develops. Older patients may have clubbing of fingers, although it is rarely observed in developed countries in the current era.

Patients with significant RVOTO may experience cyanotic spells, which are common among unrepaired patients who are older than 6 months. Many physiologic changes, such as dehydration, fever with resultant tachycardia and decrease in systemic vascular resistance may decrease relative pulmonary blood flow and trigger a cyanotic spell. Although infundibular spasm has been thought to cause cyanotic spells, this hypothesis is currently not supported. A cyanotic spell typically lasts 15 to 60 min. A long-lasting spell may result in brain damage or even death. Administration of vasoconstrictors, β-blockers, volume and sedation may be critical for stabilization. Older patients with severe cyanosis may assume a typical "squatting" position. The physiologic consequence of this posture is the increase in systemic vascular resistance with subsequent improvement in pulmonary perfusion and with left-to-right shunting across the VSD.

## PHYSICAL EXAMINATION

The presence of cyanosis and a systolic ejection murmur along the left upper sterna border is the common characteristics of moderate-to-severe form of TOF in neonates and infants. A shorter ejection murmur may indicate severe RVOTO, which may correlate with the severity of cyanosis. The second heart sound is typically single and of normal intensity. A continuous murmur may be audible when the arterial duct is patent. The parasternal RV impulse may be increased and a thrill may be palpable. Patients will usually have a normal growth pattern, although growth may be delayed if patients with associated syndromes such as DiGeorge syndrome, 22q11 deletion and trisomy 21. In such circumstances, various degrees of facial dysmorphism are also common. Infants with TOF who have minimal or mild RVOTO may have clinical features of congestive heart failure, such as tachypnea, hepatomegaly, and poor weight gain. The parasternal impulse may be increased.



**FIGURE 68-2** Chest radiograph showing a "boot-shaped heart," with upturned apex of the heart and pulmonary concavity at the upper left heart border.

## DIAGNOSTIC INVESTIGATIONS

Radiographic findings in patients with moderate-to-severe forms of TOF include decreased pulmonary vascular markings, upturned apex of the heart and pulmonary concavity of the upper-left cardiac border. The latter two features form a "boot-shaped heart" on a chest radiograph (Fig. 68-2). A right aortic arch can be found in up to 15 percent of the patients with TOF. In acyanotic infants with TOF CXR may be normal or may have signs of increase in pulmonary blood flow, such as cardiomegalyand increase in pulmonary vascular markings. The electrocardiogram usually shows normal sinus rhythm, rightward QRS axis, and various degrees of RV hypertrophy.

Echocardiography is by far the most important and effective diagnostic modality for detailing anatomic features of TOF. Nature and degree of RVOTO and deviated infundibular septum can be well documented by the subcostal right anterior oblique view (Fig. 68-3). The degree of aortic override and presence or absence of straddling of the mitral or tricuspid valve apparatus can be assessed in the parasternal long-axis view (Fig. 68-4A). Type of the VSD and presence or absence of additional muscular VSDs should be screened by multiple views (Fig. 68-4B). Other important structures to be assessed include size and morphology of the PV, size of main and branch PAs, and the presence or absence of an arterial duct. Detection of an anomalous coronary artery (anomalous origin of the left anterior descending artery or a large coronal branch of the right coronary artery crossing the RVOT) is

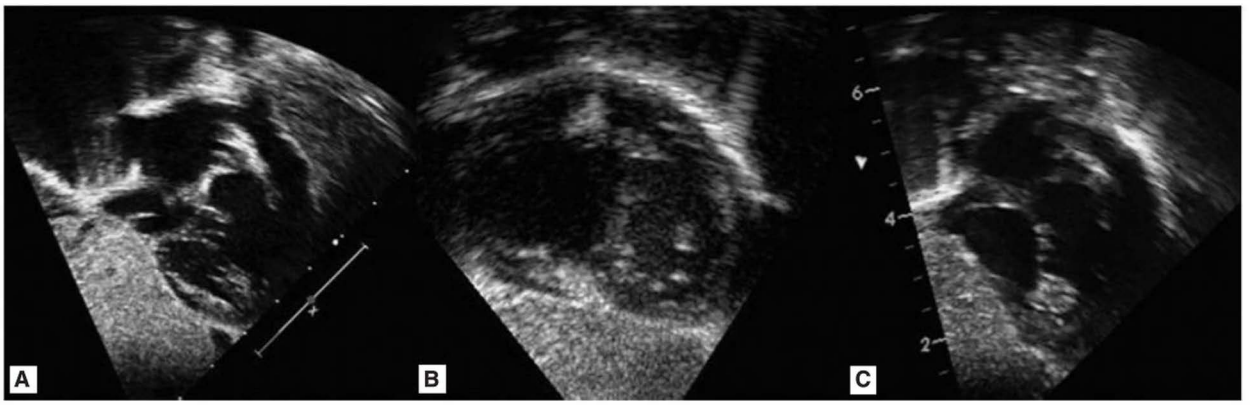



**FIGURE 68-3** **A.** Subcostal right anterior oblique echocardiographic view in a patient with mild form of tetralogy of Fallot. The anterior deviation of the infundibular septum is mild. This patient underwent repair with sparing of the pulmonary valve. **B.** Significant anterior deviation of the infundibular septum, resulting in highly obstructed subpulmonary chamber; the pulmonary valve annulus is, however, of adequate diameter. This patient underwent repair with a main pulmonary artery and infundibular patch and preservation of the PV. **C.** Diffusely hypoplastic right ventricular outflow tract and pulmonary valve with significant anterior deviation of the infundibular septum. This patient required a transannular patch at the time of surgical correction.

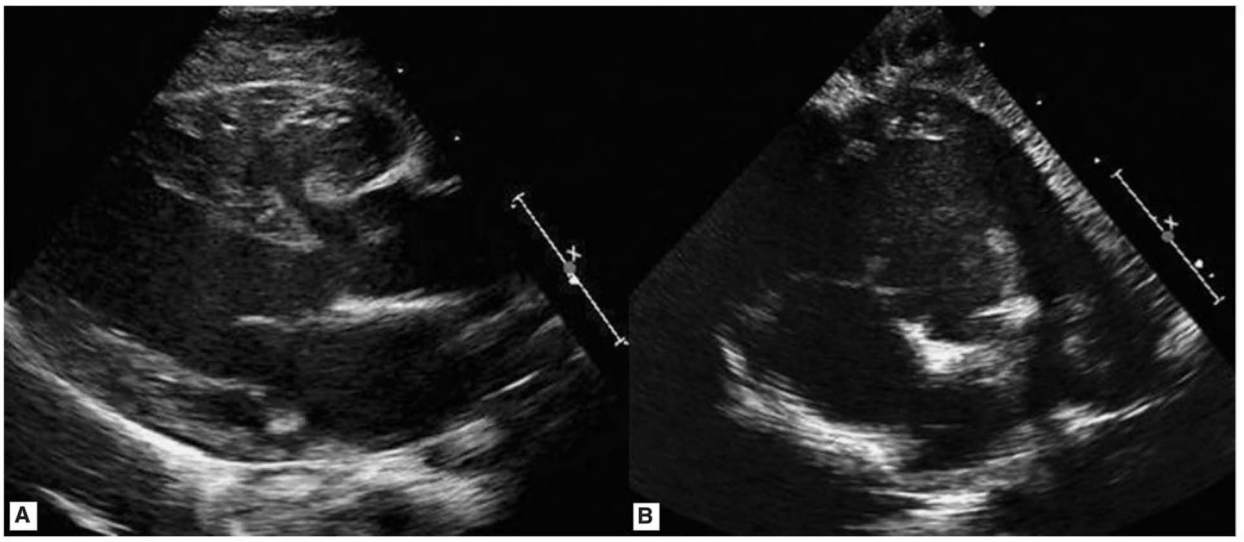



**FIGURE 68-4** **A.** Parasternal long-axis echocardiographic view showing aortic override and VSD. **B.** A large perimembranous VSD with a long infundibular chamber in a short-axis view.

of great importance for surgical decision-making and can be usually achieved by echocardiography. Aortopulmonary collateral arteries may be visualized if they are present and relatively large in size, but require delineation by angiography or computerized tomography if suspected.

Since echocardiography can provide detailed anatomic and physiologic information, the role of cardiac catheterization in the diagnosis TOF is currently somewhat limited. Cardiac catheterization may be useful when the presence of large aortopulmonary collateral arteries is suspected or to delineate the PA size if they appear small on echocardiography. Cardiac catheterization has, however, an important role if percutaneous intervention is contemplated or if the branch PAs cannot be completely assessed echocardiographically or if other imaging modalities are unsuccessful or unavailable.

## MEDICAL MANAGEMENT

The major role of medical management is to stabilize or optimize the patient's condition until palliation or definitive surgical treatment is undertaken. Severely cyanotic neonates with TOF require administration of $PGE_1$ and/or intubation with mechanical ventilation. Prostaglandin may or may not be helpful in increasing pulmonary blood flow, depending on the presence or absence of a patent arterial duct. Prompt surgical or catheter-based management is required in this situation. Infants with TOF who have progressive cyanosis with or without cyanotic spells require β-blocker administration, which is usually effective to prevent recurrence. Early elective surgery is indicated if a patient requires therapy with β-blockers for progressive cyanosis or experiences a persistent fall in arterial saturation below 80 percent. Spelling patients may require intensive treatment with sedation, systemic vasoconstriction, volume repletion and β-blockade followed by urgent surgery. Acyanotic patients with TOF may not require any medical management until surgery. Patients with TOF who have minimal RVOTO and have pulmonary overcirculation may require diuretic therapy.

## SURGICAL MANAGEMENT

The diagnosis of the lesion is per se indication for surgery. There have been significant paradigm shifts in the surgical strategy for this entity over time. In the current era, there are still, however, considerable differences in surgical management among different institutions. We highlight to follow the evolution of the surgical approach to this malformation, and describe our current management strategy.

## EVOLUTION OF THE SURGICAL APPROACH TO TETRALOGY

The presence of TOF had been uniformly lethal until the introduction of the systemic-to-pulmonary shunt by Alfred Blalock in 1944 (see Chapter 58).[21] This, other forms of shunts, and closed valvotomy procedures represented the only form of therapy until C. Walton Lillehei performed the first intracardiac repair under direct vision.[22] The repair was achieved then with a large vertical right ventriculotomy (Fig. 68-5). The VSD was closed with direct suture closure technique and RVOT muscle bundle resection was performed with a specifically designed infundibulectomy scissor.

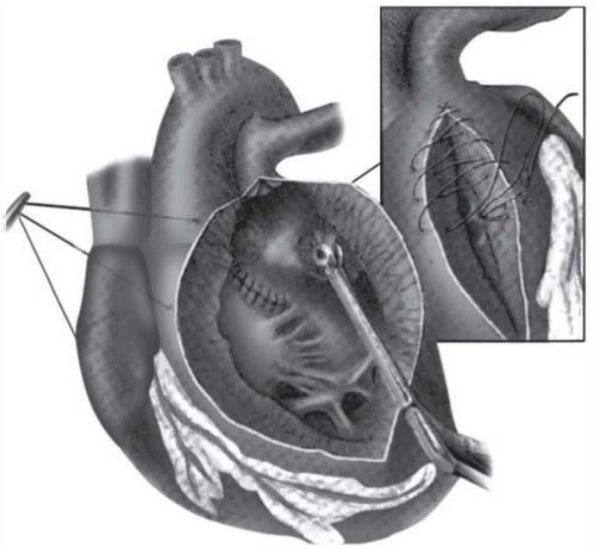


**FIGURE 68-5** Operative drawing from the original description of the first intracardiac repair of tetralogy of Fallot by the team at University of Minnesota led by C. Walton Lillehei.[22] The repair was accomplished through a large vertical right ventriculotomy under cross-circulation.

Remarkably, six of ten patients undergoing repair of TOF with parental cross-circulation survived. The role of cross-circulation was soon replaced by the heart–lung machine[23] but the fundamental concept of TOF repair through a right ventriculotomy remained. Given the early excellent results with this approach, many believed that intracardiac repair of TOF with a transannular patch and a transventricular VSD repair was a definitive repair. Over time, these patients went, however, on to develop RV dilatation, tricuspid insufficiency, atrial and ventricular arrhythmias, dysfunction and sudden death.[24,25]

A transatrial approach for repairing TOF was first reported by Hudspeth in 1963.[26] This approach was later popularized by Edmunds[27] and Kawashima,[28] who reported successful early survival, superior pulmonary competence and RV performance in a substantial number of patients. These excellent results were reproduced in high-volume centers and extended to include patients with additional anatomical abnormalities such as abnormal coronary arteries.[29]

The transatrial approach to VSD closure may better preserve RV geometry by avoiding a large right-ventriculotomy even if the pulmonary annulus is crossed. Residual mild-to-moderate RVOT stenosis with a preserved PV annulus and PV competency may be better at preserving long-term RV performance in those patients with favorable anatomic substrate. RV hypertrophy in the setting of residual stenosis may play a protective role against the dilatation associated with significant pulmonary insufficiency, thereby preserving long-term RV geometry and function.

## TREATMENT ALGORITHM—THE HOSPITAL FOR SICK CHILDREN, TORONTO

Our current management algorithm is shown in Figure 68-6. Asymptomatic patients with TOF are electively operated at 5 to 6 months of age. Earlier repair is indicated when arterial saturation ($SaO_2$) falls below 80 percent, or if the patient experiences one or more cyanotic spells. The strategy for critically cyanotic neonates is based on body weight and on the presence or absence of risk factors that may preclude neonatal repair. Neonates whose body weight is greater than 2.3 kg undergo primary repair unless a contraindication is present. The contraindications for primary neonatal repair include body weight less than 2.3 kg, prematurity below 36 weeks, pathologic biventricular hypertrophy, intracranial hemorrhage, sepsis/infection, and significant end-organ dysfunction. The neonates who are not suitable for primary repair are assessed for possible catheter-based intervention. Balloon dilatation and/or placement of RVOT stent are performed in these cases if feasible. Patients who are palliated by RVOT dilation or stent placement undergo elective repair at 3 to 6 months of age, or earlier if $SaO_2$ decreases below 80 percent. The patients who are not suitable for surgery or catheter-based intervention are kept on $PGE_1$ until the patients' growth approaches 2.5 kg or the factor(s) precluding surgery are no longer present. Our policy is to avoid the placement of a Blalock-Taussig shunt in the neonatal period or in early infancy because of the known incidence of significant pulmonary overcirculation, PA distortion, shunt thrombosis, and seromas.[30] In our experience and with this approach, primary repair has resulted in less than 1 percent morality over the past 15 years.

### Surgical Techniques

The operation is performed under mild hypothermic cardiopulmonary bypass with bicaval venous cannulation. A transatrial and transpulmonary repair[29] is our preferred approach. A right atriotomy is made parallel to the AV groove and the VSD and RVOT are exposed through the tricuspid valve orifice. The moderator band is identified. The abnormal muscle bundles crossing from the "10 o'clock" position on the tricuspid valve annulus and extending to the PV are divided and resected to increase the infundibular chamber size (these are known as the parietal muscle bundles) (Fig. 68-7A). Care is taken that the resection area does not get too close to the infundibular septum or aortic valve. Once the muscle resection is completed, the subpulmonary area is inspected to see if there is adequate volume. The VSD is closed with a Dacron patch (Fig. 68-7B). Glutaraldehyde-treated autologous or bovine pericardium or polytetrafluoroethylene can also be used as patch materials. If the infundibular chamber size is small but the PV size is adequate, an infundibular outflow patch is added to achieve an unobstructive sub-valvar outflow tract. The size of the

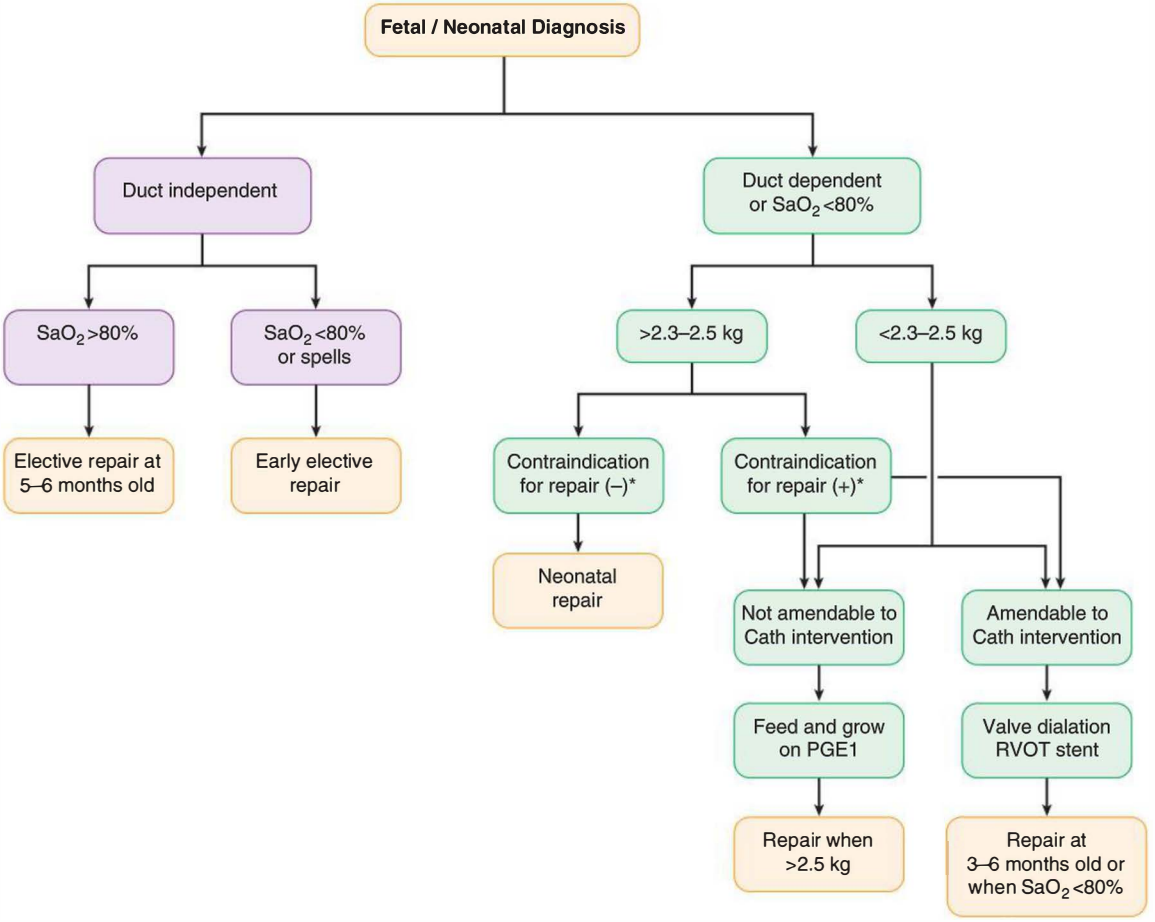



**FIGURE 68-6** The treatment algorism for patients with tetralogy of Fallot at The Hospital for Sick Children in Toronto. $PGE_1$, prostaglandin $E_1$; $SaO_2$, arterial saturation.*Contraindications: body weight less than <2.3 to 2.5 kg, significant prematurity, pathologic ventricular hypertrophy, intracranial hemorrhage, sepsis/infection, and significant end-organ dysfunction.

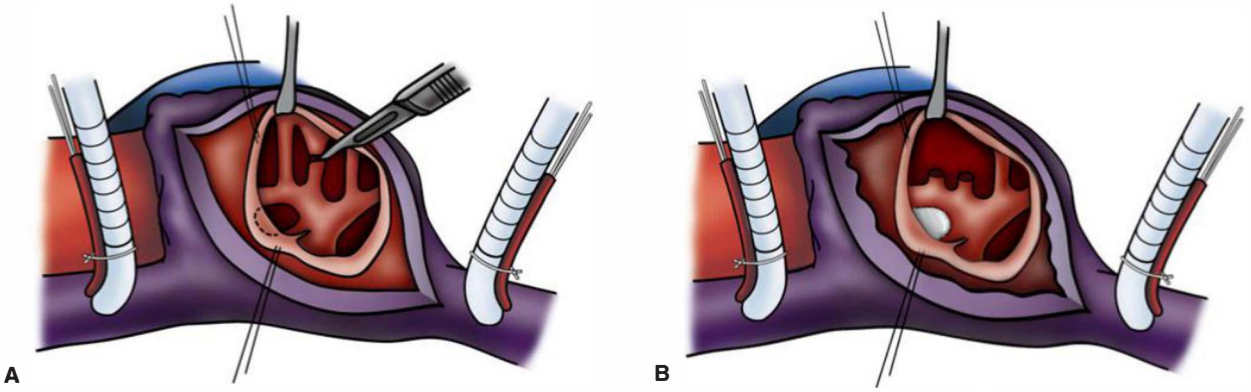



**FIGURE 68-7** **A.** Right ventricular outflow tract muscle resection in tetralogy of Fallot repair. The septomarginal trabeculation and moderator band are identified. The septoparietal trabeculations that arise from the septomarginal trabeculation to RV free wall should be resected. In addition, hypertrophied RV free wall can be resected. **B.** The VSD is closed with a continuous suture technique. Suspension stitches placed on the anterior and septal leaflets of the tricuspid valve facilitate exposure.

ventriculotomy is kept small, typically, so that it would not allow for VSD closure via the incision.

### PULMONARY VALVE PRESERVATION STRATEGY

In general, the PV can be preserved if the annulus size is more than 70 to 80 percent of normal. Our strategy to maximize the possibility of PV preservation is to perform a stepwise RVOT construction. A valvotomy and commissurotomy are performed on the PV through a vertical main pulmonary arteriotomy and the main PA and two PV sinuses are enlarged with a patch (Fig. 68-8A and B). The functional assessment of residual RVOTO is performed after weaning from cardiopulmonary bypass by intraoperative transesophageal echocardiogram and direct needle pressure measurement. An RV systolic pressure less than 75 percent of systemic pressure is accepted (for a 5–6-month old this is usually around a systolic RV pressure of 50–55 mm). If the RV systolic pressure is subsystemic and there is infundibular stenosis, an additional infundibular patch is placed (Fig. 68-8C and D). If a significant obstruction remains at the level of the PV annulus after placing the infundibular patch, a limited transannular patch is placed (Fig. 68-8E and F). With this approach, the PV annulus is preserved in approximately 80 percent of the patients. Other strategies (including intra-operative balloon pulmonary anuloplasty) have been recently introduced to preserve function of the PV.[31]

## Controversies in Surgical Strategy

Acyanotic infants with TOF undergo elective surgical repair between 5 and 6 months of age (Fig. 68-6); this approach is based on the notion that infants <6 months of age generally have good physiologic tolerance to surgical intervention, can have their atrial defect closed, and are proven to have prompt postoperative recovery with less inotropic and fluid requirement when compared to small infants less than 3 months of age.[32] Timing of surgery for asymptomatic patients in other centers varies from the neonatal period to around 1 year of age.[33,34] The surgical strategy for cyanotic neonates with TOF varies more markedly among different centers. We[6] and other centers[35,36] advocate primary repair for symptomatic neonates unless contraindicated. Dilation or stenting of the RVOT is the second option if infants have risk factors precluding primary neonatal repair (Figs. 68-6 and 9).[30,37] Some centers will routinely place a modified Blalock-Taussig shunt in the neonatal period followed by complete repair.[34] A recent series showed equivalent survival between the two strategies in symptomatic neonates with TOF.[38]

Many centers, including ours, advocate a transatrial transpulmonary approach, although some still prefer transventricular approach. The major advantage of a transatrial approach is the potential avoidance of a ventriculotomy and of a large transannular patch. Potential advantages of transventricular approach include better exposure and ability to enlarge the hypoplastic infundibulum without extensive muscle resection, which may result in extensive endocardial scar formation.[39]

Less than 2 percent of infants have insufficient PA size for complete repair. In these infants shunts, transannular patches and/or percutaneous interventions are used to induce PA growth prior to repair.[40,41]

# EARLY OUTCOME

Operative mortality of TOF repair was as high as 25 percent in the 1960s and 1970s, improving to less than 10 percent by the 1980s.[42,43] In the current era, primary repair for acyanotic TOF can be done with a mortality of less than 1 percent.[6,34] Even among symptomatic neonates or small infants undergoing primary repair, the hospital mortality ranges from 1 to 3 percent in contemporary series.[35,36] Classic risk factors for operative death included small PV and annular size, high postrepair RV/LV pressure ratio and young age at repair[43]; these risk factors have largely been overcome in the current era. Most patients undergoing elective repair will quickly recover, with prompt weaning from mechanical ventilation and intensive care unit stay of less than 48 hours.[32] Up to one-third of the patients will, however, have significant low cardiac output state due to the restrictive physiology of the RV.[44]

## Restrictive Physiology of the Right Ventricle

Some postrepair TOF patients develop poor diastolic relaxation of the RV that causes the ventricle to function as a passive conduit in diastole rather than as a compliance chamber. This can lead to a low cardiac output state, requiring significant fluid resuscitation. This situation is known as restrictive physiology and is characterized by the presence of antegrade late diastolic flow in the PA as seen by pulse Doppler echocardiography (Fig. 68-10). This indicates that the atrial contraction is directly transmitted to the PA. Systolic function is usually maintained. Treatment includes spontaneous ventilation or minimal airway pressure ventilation with minimal airway pressure. This in turn facilitates blood flow through the RV, as does maintaining a high preload with a central venous pressure of up to 15 mm Hg or more; additional therapeutic measures include complete drainage of both pleural spaces and the abdominal cavity and, in severe cases, reopening of the chest to improve diastolic filling. Inotropic support should be minimized. The phenomenon is common in patients who had a transannular patch repair.[45] Although restrictive physiology is associated with significant early postoperative morbidity, it paradoxically is related to less late QRS prolongation, less cardiomegaly and improved exercise tolerance at late follow-up.[45,46]

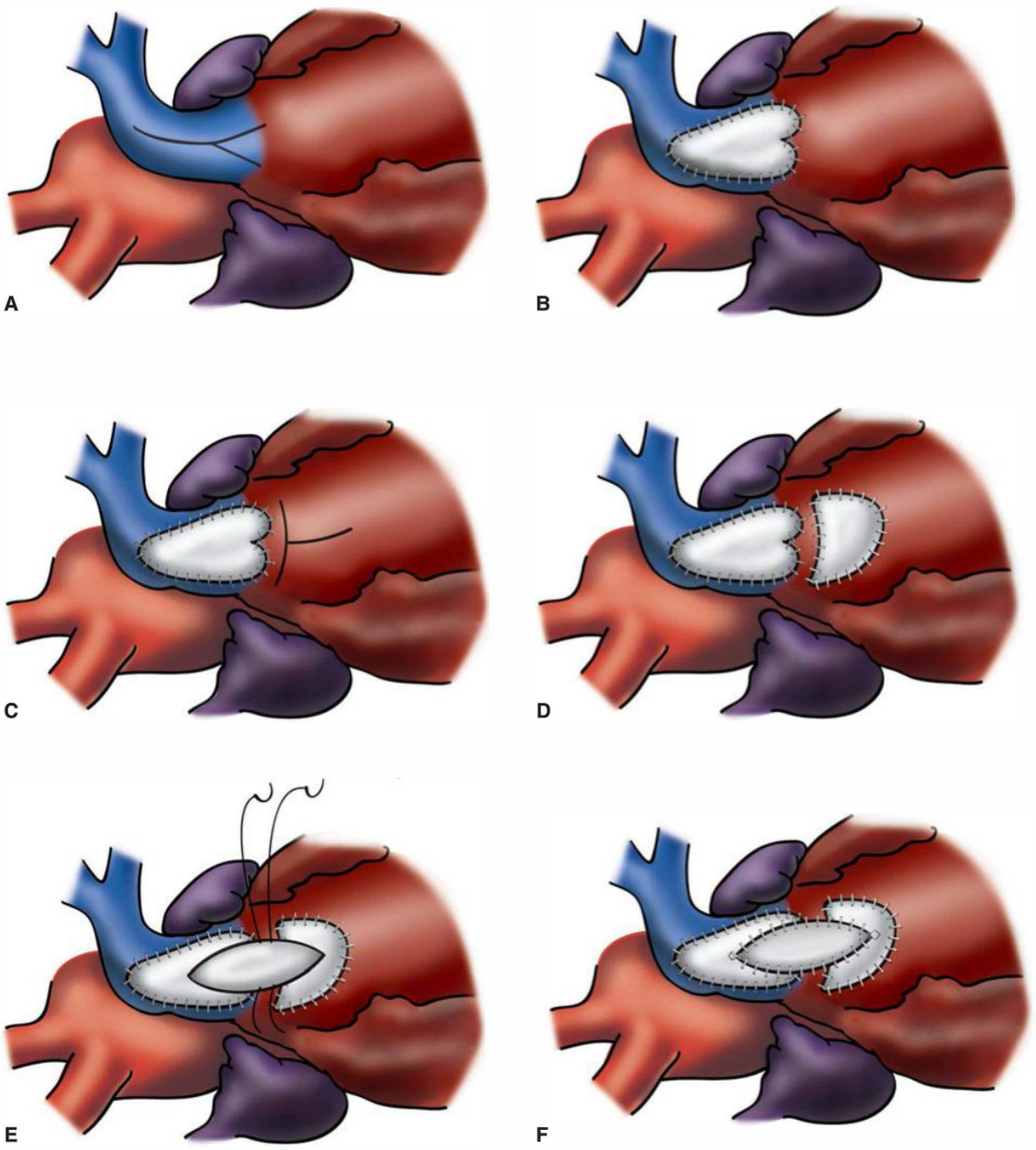



**FIGURE 68-8** **A.** The first step of right ventricular outflow tract reconstruction. A vertical incision on the main pulmonary artery is extended into two pulmonary sinuses. **B.** The main pulmonary artery and two pulmonary sinuses are enlarged either with a fresh pericardial or a polytetrafluoroethylene patch. **C.** If residual right ventricular outflow tract obstruction persists after main pulmonary artery patch repair, the infundibular chamber is enlarged with a limited infundibular incision. **D.** A polytetrafluoroethylene patch is placed just below the pulmonary valve annulus. **E.** If significant obstruction remains at the annulus level after two-patch repair, a limited transannular patch is placed by cutting across the patches and the annulus. **F.** A polytetrafluoroethylene patch is placed across the pulmonary valve annulus.

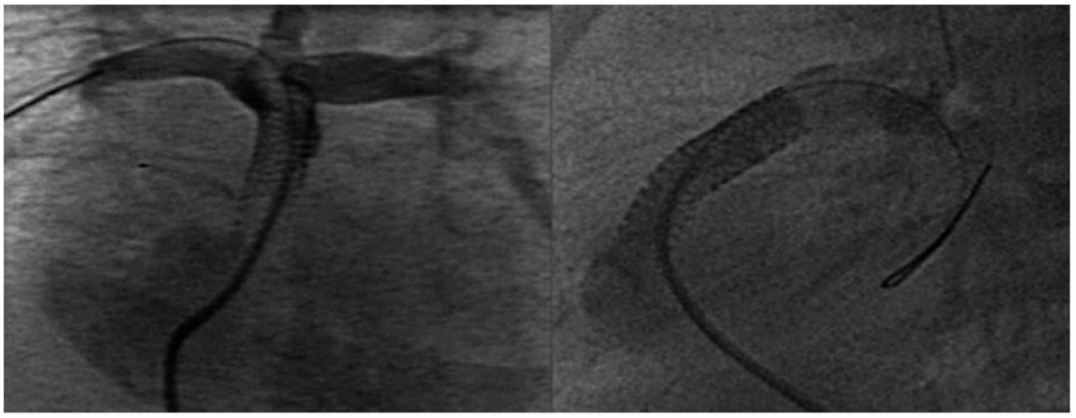


**FIGURE 68-9** Stent placement across the stenotic right ventricular outflow tract and pulmonary valve annulus in a severely cyanotic neonate with tetralogy of Fallot. (Courtesy of Dr. Lee Benson in The Hospital for Sick Children, Toronto.)

## LATE OUTCOME

Large surgical series from several centers as well as from our institution have shown an overall 85 to 87 percent survival rate at 30 years after repair.[42,47,48] The constant risk of death is approximately 0.3 percent/year in the first 30 years after repair. The Mayo clinic group showed older age at operation and a high postrepair RV/LV systolic pressure ratio as independent risk factors for late mortality on multivariate analysis.[47] Conflicting results have been reported regarding the impact of transannular patch on long-term survival: data from the Toronto group showed no difference in late survival between transannular patch and valve-sparing repair,[42] whereas others suggested a negative impact of a transannular patch on long-term outcomes.[48] The most common mode of late death is cardiac-related sudden death, followed by congestive heart failure and death related to reoperations. In the current era of very low early mortality, 40-year survival can be estimated to be nearing 90 percent.[42]

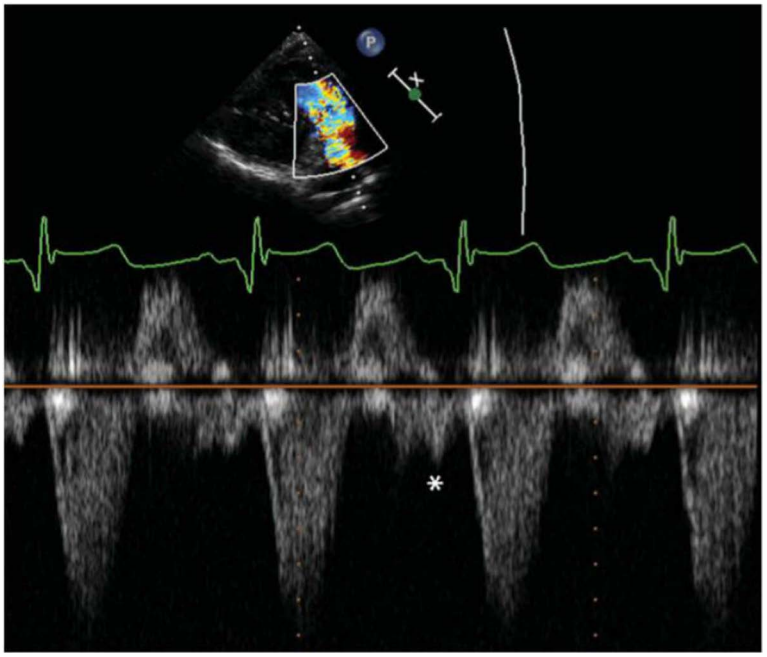



**FIGURE 68-10** The restrictive pattern of the RV seen by pulse Doppler echocardiography. Antegrade late diastolic flow in the pulmonary artery is shown.

The functional status of the long-term survivors is reasonable: approximately 80 percent of patients are in New York Heart Association (NYHA) functional class I, and less than 10 percent are in class III at median follow-up of 30 years.[47] Nonetheless, exercise capacity of these patients is markedly impaired. Maximal oxygen consumption among postrepair TOF patients whose are in NYHA class I is approximately two-thirds of the predicted value. Decrease in exercise capacity is strongly related to the magnitude of pulmonary insufficiency[49] as well as with the degree of biventricular dysfunction.[50]

## Late Problems and Management

Patients with TOF will still have life-long residual anatomic and functional problems (see Chapter 90). The major possible residual lesions include significant pulmonary insufficiency and subsequent RV dilatation and dysfunction, residual VSD or atrial septal defect, tricuspid valve regurgitation, residual RVOTO or aneurysm formation, branch PA stenosis and atrial and/or ventricular arrhythmias. This patient group therefore necessitates long-term follow-up by a comprehensive team that is well versed in the specific care of adults with CHD. Up to one-sixth of patients will at some point require reoperation. Indications for reoperation, as summarized by the Canadian Cardiovascular Society[51] are shown in Table 68-1.

**TABLE 68-1: Indication for Reoperation in Patients with Repaired TOF**

**Indication for reoperation**

1. Free pulmonary regurgitation associated with
   - Progressive or moderate-to-severe RV enlargement (RV end-diastolic volume >170 mL/m²)
   - Moderate-to-severe RV dysfunction
   - Important TR
   - Atrial or ventricular arrhythmias
   - Symptoms such as deteriorating exercise performance
2. Residual VSD with $Q_p/Q_s$ > 1.5:1
3. Residual pulmonary stenosis with RV pressure at least >2/3 systemic pressure
4. Significant AI with symptoms and/or progressive LV dysfunction
5. Aortic root enlargement >55 mm
6. A large RVOT aneurysm or evidence of infection or false aneurysm
7. Sustained atrial flutter or fibrillation, or sustained ventricular tachycardia
8. Combination of residual VSD and/or residual pulmonary stenosis and regurgitation

Data from Silversides CK, Kiess M, Beauchesne L, et al. Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease: Outflow tract obstruction, coarctation of the aorta, tetralogy of Fallot, Ebstein anomaly and Marfan syndrome. *Can J Cardiol* 2010 Mar;26(3): e80–e97.

### PULMONARY INSUFFICIENCY, RIGHT VENTRICULAR DYSFUNCTION AND PULMONARY VALVE REPLACEMENT

As the clinical significance of pulmonary insufficiency increases overtime following TOF repair, so does RV chamber size and compliance.[52] Progressive dilatation can result in a decrease in systolic function. At a certain point, these changes become irreversible even if volume overload is eliminated by pulmonary valve replacement (PVR). The risk of requiring PVR is constant and is approximately 0.8 percent/year over 30 years.[42] Our series of PVR in patients with severely dilated (mean RV end-diastolic volume index of 227 mL/m²) and dysfunctional RVs showed that PVR failed to reverse RV dilatation and RV systolic function.[53] No RV that had an end-diastolic volume >180 mL/m² had remodeling to a normal size subsequent to PVR.[54] It is therefore important to timely intervene with PV implantation while RV dilatation and dysfunction are still reversible. As shown in Table 68-1, our current criteria for PVR include RV end-diastolic volume >170 mL/m², moderate-to-severe RV dysfunction, QRS duration >180 msec, and/or decrease in exercise tolerance. A decision for borderline patients who meet some but not all of these criteria is still subjective. We prefer to see at least two criteria met. When performed before irreversible dysfunction occurs, PVR improves symptoms and decreases RV end-diastolic and end-systolic volumes. Ejection fraction of the RV generally does not change significantly after PVR.[54] RV remodeling surgery, that is, surgical plication of the noncontractile portion of RV at the time of PVR may improve RV ejection fraction in these patients.[55] There is some but not strong evidence to show improved exercise tolerance after PVR.[56] There is no clear benefit of PVR on survival, and recent studies show that PVR does not reduce the risk of ventricular tachycardia and death compared to matched controls.[57] Percutaneous PV insertion is an alternative option, but is currently limited to patients whose PV annulus is 22 mm in diameter or smaller.[51] Survival after PVR is 92 to 95 percent at 5 years and 76 to 86 percent at 10 years.[54,58]

### ANATOMIC RESIDUAL LESIONS

Up to 15 to 20 percent of patients who require late reoperation do so for reasons other than pulmonary regurgitation.[47] The next most frequent lesions are residual VSD and recurrent/residual RVOTO.[42,47,48] Indication for residual VSD closure is a $Q_p/Q_s$ > 1.5:1 or the presence of residual VSD with $Q_p/Q_s$ <1.5:1 with significant pulmonary stenosis or regurgitation. Surgical indication in case of RVOTO is an RV systolic pressure chronically greater than two-thirds of the systemic (Table 68-1). Branch PA stenosis is also common in repaired patients, and is typically managed by balloon angioplasty and/or stent placement. It is rare for isolated branch PA stenosis to require surgical intervention; patch enlargement for stenotic branch PA is, however, undertaken as a concomitant procedure at the time of PVR or intervention for RVOTO. Severe symptomatic tricuspid regurgitation (TR) can be an isolated

indication for surgery. More importantly, TR that is more than mild-to-moderate should be treated at the time of PVR.

### ARRHYTHMIAS AND SUDDEN DEATH

The incidence of arrhythmias late after TOF repair is substantial: Forty-three percent of patients have sustained arrhythmias at 30 years after complete correction.[59] Atrial arrhythmias are present in 20 percent of patients and are mainly represented by atrial reentrant tachycardia, followed by atrial fibrillation. Predictors for the development of atrial arrhythmias on multivariate analysis include reduced left ventricular ejection fraction, older age, number of cardiac surgical interventions, hypertension and right atrial enlargement.[59] Pharmacological therapy including β-blocker, digoxin, and amiodarone is the first line of therapy. Surgical cryoablation or right-sided Maze procedure[60] at the time of PVR or other reoperations is an effective means to reduce the risk of recurrence of atrial arrhythmias.[61]

Ventricular tachycardia occurs in 15 percent of patients during the same time interval. They are mainly treated with amiodarone and β-blockers. Approximately 10 percent of patients will subsequently require placement of an implantable cardioverter defibrillator for ventricular tachycardia refractory to medical treatment. Independent risk factors for ventricular tachycardia on multivariate analysis include number of cardiac surgeries, long QRS duration and reduced left ventricular diastolic function. Intraoperative electrophysiological mapping and surgical ablation is an option in patients with ventricular arrhythmias associated with pulmonary insufficiency and RV dilatation/dysfunction.[61] As mentioned above, PVR transiently shortens the QRS interval if the preoperative QRS duration is <180 msec; this effect is usually not long-lasting. Overall incidence of sudden cardiac death is <0.2 percent. Prolonged QRS (greater than 180 ms) has been implicated as a risk factor for sudden death;[62] however, large studies have failed to show that QRS duration was an independent risk factor for sudden death due to relatively small number of events.

A permanent pacemaker for late conduction disturbance is necessary in 2 to 3 percent of patients.[48,59] Indications for implantation include AV block (66 percent), sinus node dysfunction (18 percent) and tachycardia/bradycardia syndrome (16 percent).[59]

Cardiac resynchronization therapy may improve RV function, and clinical studies have shown improved right and left ventricular function following institution of biventricular pacing.[63]

## TETRALOGY OF FALLOT WITH ABSENT PULMONARY VALVE SYNDROME

A minority of patients (3 percent) with TOF have only rudimentary or absent PV leaflets. This anatomical feature of the PV is usually associated with markedly dilated main and branch PAs.[18,64] Such massively dilated PAs frequently cause bronchial compression and bronchomalacia.[65] The intracardiac anatomic features are essentially similar to typical TOF. Patients with TOF/absent PV do also typically not have an arterial duct at birth.[66,67] Two clinical forms of TOF/absent PV have been described: (1) patients who present predominantly with respiratory distress in early infancy; (2) patients who present with cyanosis similar to classic TOF. About two-thirds of the patients have respiratory symptoms due to bronchial compression, and 40 percent of them will do so in early infancy, requiring urgent surgical intervention.[65] Some patients need preoperative mechanical ventilation or even extracorporeal membrane oxygenation (ECMO).[68] Transthoracic echocardiography is sufficient enough to visualize the intracardiac structures and abnormalities; however, additional tomographic or magnetic resonance imaging (MRI) demonstrates the degree and extension of bronchial compression and its relation to the PAs.

Early primary repair is indicated when neonates and infants present with moderate or severe respiratory symptoms. Patients with minimal or mild respiratory symptoms are treated according to standard TOF treatment algorithms. The goals of surgical repair for symptomatic infants are to relieve bronchial compression by aggressive reduction of the dilated branch and main PA and to reestablish competency of the PV. During surgical correction, a strip of the dilated PAs is resected from hilum to hilum. Transection of the ascending aorta helps to expose the entire central PA.[69] Mobilization, suspension, and even anterior translocation (Lecompte maneuver) may be necessary in addition to PA size reduction to relieve bronchial compression.[70] Our preference is to use a homograft or bovine jugular vein valved conduit to achieve PV competency, whereas some centers routinely use a transannular patch as a method of RVOT reconstruction. Our clinical experience with 61 patients with TOF/absent PV operated between 1982 and 2006 has shown a survival of 93 percent at 5 years and 87 percent at 10 years after repair. All three operative deaths in this series (5 percent) occurred in neonates with severe bronchial compression. Reoperation is common (up to 40 percent at 10 years), and is mainly required because of structural failure of the RV-PA conduit or somatic overgrowth of the conduit by the patient.

## TETRALOGY OF FALLOT WITH ATRIOVENTRICULAR SEPTAL DEFECT

Up to 2 percent of patients with TOF have anatomic features of AVSD (see Chapter 66). In addition to anterior deviation of the infundibular septum and RVOTO, these hearts disclose ventricular inlet abnormalities, namely common AV junction with a common AV valve.[71] A large VSD with inlet extension is present. The inlet abnormality makes the left ventricular outflow unwedged and narrowed ("goose neck" appearance on the angiogram). Approximately 80 percent of patients with TOF/AVSD will have trisomy 21.[72] The direction of the shunt at the ventricular level can be from left to

right, bidirectional, or predominantly right to left depending on the degree of RVOTO. The direction of shunt at the atrial level through the ostium primum defect is typically from left to right, but it can be bidirectional because of hypertrophy and diminished compliance of the RV. Most patients with TOF/AVSD present with cyanosis rather than congestive heart failure.[71,72]

The classic surgical strategy utilized in infants with TOF/AVSD has been a staged repair, with initial placement of a systemic-to-pulmonary shunt and subsequent late repair. The systemic-to-pulmonary shunt improves saturation and may facilitate growth of both AV valves by inducing volume overload.[73] However, it may potentially worsen AV valve insufficiency as well as ventricular hypertrophy, which may complicate definitive repair. Our current approach is to perform primary repair after 3 or 4 months of age, although we would prefer for the infant to reach 6 to 8 months of age if possible. The left AV valve in a cyanotic infant with TOF/AVSD can be quite small due to low $Q_p/Q_s$. If there are additional anatomic risk factors, such as unbalanced ventricles and AV valve orifice, poorly formed or narrowly spaced papillary muscles or preoperative significant left AV valve regurgitation, catheter-based intervention as a temporary palliation may be preferred.

The repair can be accomplished either by transventricular[72] or transatrial–transpulmonary approach.[74] The same surgical principles outlined above are applied to relieve the RVOTO; given the high prevalence of a hypoplastic infundibulum in this subgroup, up to 70 percent of the patients will require a transannular patch.[72] Our preferred approach is that of repairing the AVSD with a two-patch technique (See Chapter 66). We also prefer to maintain pulmonary competency by insertion of an RV-to-PA conduit if the native PV is of insufficient size. Intermediate-term competence can also be obtained by insertion of a polytetrafluoroethylene monocusp valve. Between 1981 and 1997, we have corrected 38 patients with this particular combination of anomalies with an early mortality of 6 percent.[72]

## SUMMARY

With appropriate understanding of the anatomy and with an appropriately aggressive treatment algorithm, most patients with TOF including symptomatic neonates survive intracardiac repair in infancy without the need for a staged approach to correction. Preservation of long-term RV function is and PV competency is of prime importance for this population in order to achieve long-term freedom from complications and need for reintervention.

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## TETRALOGY OF FALLOT BOARD REVIEW QUESTIONS (CHAPTER 68)

1. What is the essential underlying anatomic feature of tetralogy of Fallot?
   A. Anterior deviation of the infundibular septum
   B. VSD
   C. RV hypertrophy
   D. Aortic override
   E. Pulmonary stenosis

2. Which is not a correct treatment strategy for a critically cyanotic neonate with tetralogy of Fallot?
   A. Administration of $PGE_1$
   B. Intubation and mechanical ventilation
   C. Prompt surgical intervention
   D. Balloon atrial septostomy
   E. Ductal stenting

3. What is the best treatment strategy for a 1-month-old infant with TOF without cyanosis?
   A. Immediate definitive surgical repair
   B. Immediate stent placement in the RV outflow tract
   C. Observe and electively operate at 5 to 6 months of age
   D. Administration of β-blocker
   E. Creation of a systemic to PA shunt

4. What are the treatment strategies for restrictive physiology of the RV following TOF repair?
   A. Spontaneous ventilation with minimal airway pressure
   B. Volume infusion to maintain high preload
   C. Adequate drainage from pleural and peritoneal spaces
   D. Avoid inotropes
   E. All of the above

5. What is not a late problem among the long-term survivors following surgery for tetralogy of Fallot?
   A. Mitral insufficiency
   B. RV dysfunction
   C. Arrhythmias
   D. Sudden death
   E. Pulmonary stenosis

## ANSWERS

1. **Answer: D.** The anatomy of TOF is essentially determined by the anterior deviation of the infundibular septum, which results in other features such as VSD, aortic override, and RVOT obstruction. Pulmonary stenosis and RV hypertrophy are also common anatomic features of this entity.

2. **Answer: E.** Ductal stenting will increase the amount of intracardiac mixing, which does not alleviate the cyanosis. Neonates with TOF who present with critical cyanosis often have duct-dependent pulmonary circulation. Administration of $PGE_1$ is the first line treatment for this condition. If the arterial duct is not patent, urgent surgical or catheter-based intervention is required.

3. **Answer: C.** Acyanotic patients with TOF do not require immediate intervention. Elective surgery can be done at 4 to 6 months of age or when cyanosis develops. Shunting is not indicated, as the patient is not cyanotic. β-blockade is useful in patients with cyanotic spells.

4. **Answer: E.** Restrictive physiology of the RV should be treated by minimizing afterload to the RV and by maintaining adequate preload. It is important to drain pleural and peritoneal cavities. Severe cases may need chest opening to improve diastolic filling of the RV.

5. **Answer: A.** Tricuspid, not mitral, insufficiency is a late complication. Other common problems among the long-term survivors mainly stem from chronic pulmonary insufficiency and subsequent RV dilatation and dysfunction. Significant RV dilatation and dysfunction are often related to arrhythmias and sudden death.

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69

# Pulmonary Atresia with Ventricular Septal Defect and Major Aortopulmonary Collaterals

*Malcolm J. MacDonald*
*Frank L. Hanley*

**KEY CONCEPTS**

- Epidemiology
  - Pulmonary atresia (PA) with ventricular septal defect (VSD) and major aortopulmonary collaterals (MAPCAs) is a complex lesion with great morphologic variability that represents approximately 2 percent of congenital heart defects, with a prevalence of 0.07 per 1000 live births.
- Morphology
  - This particular malformation entails the association of atresia of the pulmonary valve, a tetralogy-type VSD, and pulmonary collateral vessels that usually originate from the descending thoracic aorta.
- Clinical features
  - Neonates born with PA, VSD, and MAPCAs may have very unpredictable presentation owing to the anatomic variability of the lesion. Patients may be minimally symptomatic or severely cyanotic, or may develop congestive heart failure (CHF) from pulmonary overcirculation.
- Diagnosis
  - Diagnostic evaluation includes echocardiography, cardiac catheterization, and, in selected cases, computed tomographic angiography (CTA) to clarify the anatomy of the MAPCAs.
- Treatment
  - Definitive treatment is surgical. The ultimate goal of surgical therapy is creation of separated, in-series pulmonary and systemic circulations. Achievement of this goal requires unifocalization of the vascular systems, VSD closure, and reconstruction of the right ventricular outflow tract (RVOT). "Single-stage" unifocalization with or without concurrent VSD closure is favored by the authors.
- Outcomes
  - In over 460 patients managed by the authors' protocol, complete unifocalization via median sternotomy was achieved in 76 percent of patients. Intracardiac repair (VSD closure) was possible at initial operation in 56 percent. Ninety-five percent of patients were completely repaired by 5 years of age. Recent operative mortality was 2.3 percent, with a 5-year actuarial survival of 85.5 percent.

## INTRODUCTION AND BACKGROUND

Pulmonary atresia (PA) with ventricular septal defect (VSD) and major aortopulmonary collateral arteries (MAPCAs) is a complex lesion with great morphologic variability. The lesion is characterized by atresia of the pulmonary valve, a tetralogy of Fallot-type VSD, and pulmonary collateral vessels originating from the aorta. The major variability occurs in the pulmonary vascular circulation. Development of the pulmonary arterial system occurs by fusion of the left and right sixth dorsal aortic arches with the plexus of systemic arteries carried by the lung buds from the foregut. Failure of the normal fusion process results in PA. Development of the true pulmonary arteries (PAs) is variable and depends on the point in gestation at which connection of the lumen of the true PAs with the right ventricle (RV) is lost.[1] True central

PAs vary from normal size to absent. The mean diameter of the central PAs in the author's series of over 300 patients was 1.5 mm. A small central confluence is usually present. When confluent PAs are present, there is typically no ductus arteriosus. When the right and left main PAs are discontinuous, bilateral ducti may exist with the right typically originating from the innominate or subclavian artery.

Persistent connections from the aorta (MAPCAs) probably originate from splanchnic vessels. Collaterals vary widely in origin, course, size, and histologic appearance. The mean number of collaterals in the author's series was 3.8 ± 1.4. Most commonly, aortopulmonary collaterals originate from the proximal descending aorta. There is great variability in the way in which MAPCAs connect to the pulmonary circulation. A given lung segment may have its blood supply uniquely derived from the true PA system, MAPCAs, or both; collateral vessels may supply anything from a small proportion of the total lung parenchyma to the majority of the pulmonary vascular bed. Variable degrees of obstruction of the collateral vessels may occur, and obstructions may be inconsistent in their location—proximally or distally—within the vessels. Diffuse collateralization from the systemic circulation, especially the chest wall, is common, particularly after surgical intervention.

The pulmonary microcirculation is the healthiest at birth, and declines progressively afterward. The natural history of the MAPCAs is to frequently progress to stenosis, which may in turn result in distal microvascular hypoplasia. In the absence of stenosis, the systemic pressure within the pulmonary vasculature may cause pulmonary vascular obstructive disease (PVOD). Surgical interventions requiring the use of systemic-to-PA connections (e.g., Blalock–Taussig shunt or aortopulmonary window) may also result in PVOD due to the persistence of pulmonary vascular flow at systemic pressure.

The intracardiac anatomy is typified by an anteriorly malaligned VSD (hence the alternative designation as tetralogy of Fallot with PA). Although the ventricles are typically normally developed, the infundibulum of the RV may be quite small. There are normal atrioventricular and ventriculoarterial connections (Fig. 69-1).

## EPIDEMIOLOGY, MORPHOLGY, AND ASSOCIATED ANOMALIES

PA with VSD represents approximately 2 percent of congenital heart defects. In the Baltimore–Washington Infant Study, a prevalence of 0.07 per 1000 live births was reported.[2] PA with VSD accounted for 1.4 percent of all forms of congenital heart disease, and 20.3 percent of all forms of tetralogy of Fallot. Of patients with PA and VSD, approximately 60 percent have a ductus arteriosus and normal branch PAs, and 40 percent have MAPCAS. Infants of overtly diabetic mothers are at approximately 10-fold risk of developing PA with VSD. Genetic factors are considered likely to be etiologically contributory, since an increased risk of occurrence to siblings (2.5–3 percent) or to children of parents with tetralogy of Fallot (1.2–8.3 percent) has been observed.

Associated cardiac and extracardiac anomalies may occur. Commonly associated cardiac anomalies include secundum atrial septal defects, coronary anomalies, and multiple VSDs. Other less common cardiac anomalies may also occur.

A significant proportion of patients with PA and VSD have associated syndromes or extracardiac anomalies. Such associations include the VATER syndrome, Alagille syndrome, DiGeorge (velocraniofacial) syndrome, and trisomy 21 among others. There may be an unusually high incidence of tracheobronchial anomalies, particularly the origin of the right upper lobe bronchus from the trachea, which may result in postoperative respiratory complications involving the right upper lobe.

## CLINICAL FEATURES

Children born with PA, VSD, and MAPCAs may have very unpredictable presentation due to the anatomic variability of the lesion. Approximately 80 percent are minimally symptomatic, and have only mild cyanosis. The VSD is typically unrestrictive. Patients with valvar atresia but little collateralization may be severely cyanotic. Patients with severe atresia and/or hypoplastic true PAs but extensive collateralization may be minimally symptomatic and plethoric. Such patients may eventually develop congestive heart failure (CHF) due to pulmonary overcirculation, or may develop progressive cyanosis. Cyanosis occurs due to paucity of pulmonary flow because of inadequate collaterals, stenosis of the collaterals, or pulmonary microvascular obstructive disease. Development of these complications may occur at very variable rates, resulting in unpredictably delayed presentation. Cyanotic spells may occur. In patients with PA these occur due to decreases in systemic vascular resistance resulting in markedly decreased pulmonary blood flow [rather than due to RV infundibular spasm, as is usual in tetralogy without atresia]. Late presentation may occur[3] and may include polycythemia, "clubbing," cerebral embolism, and cerebral abscesses.

## DIAGNOSTIC EVALUATION

Following presentation with the symptoms described above, patients require complete diagnostic investigation. Pulse oximetry is a useful indicator of adequacy of pulmonary blood flow. Patients with oxygen saturation greater than 85 to 90 percent will typically have well-developed collateral systems and are at risk for CHF. Patients with oxygen saturations of less than 75 to 80 percent may have poorly developed pulmonary vascular and collateral systems.

Chest radiographs may demonstrate pulmonary plethora or hypoperfusion of the lung fields. The electrocardiogram is

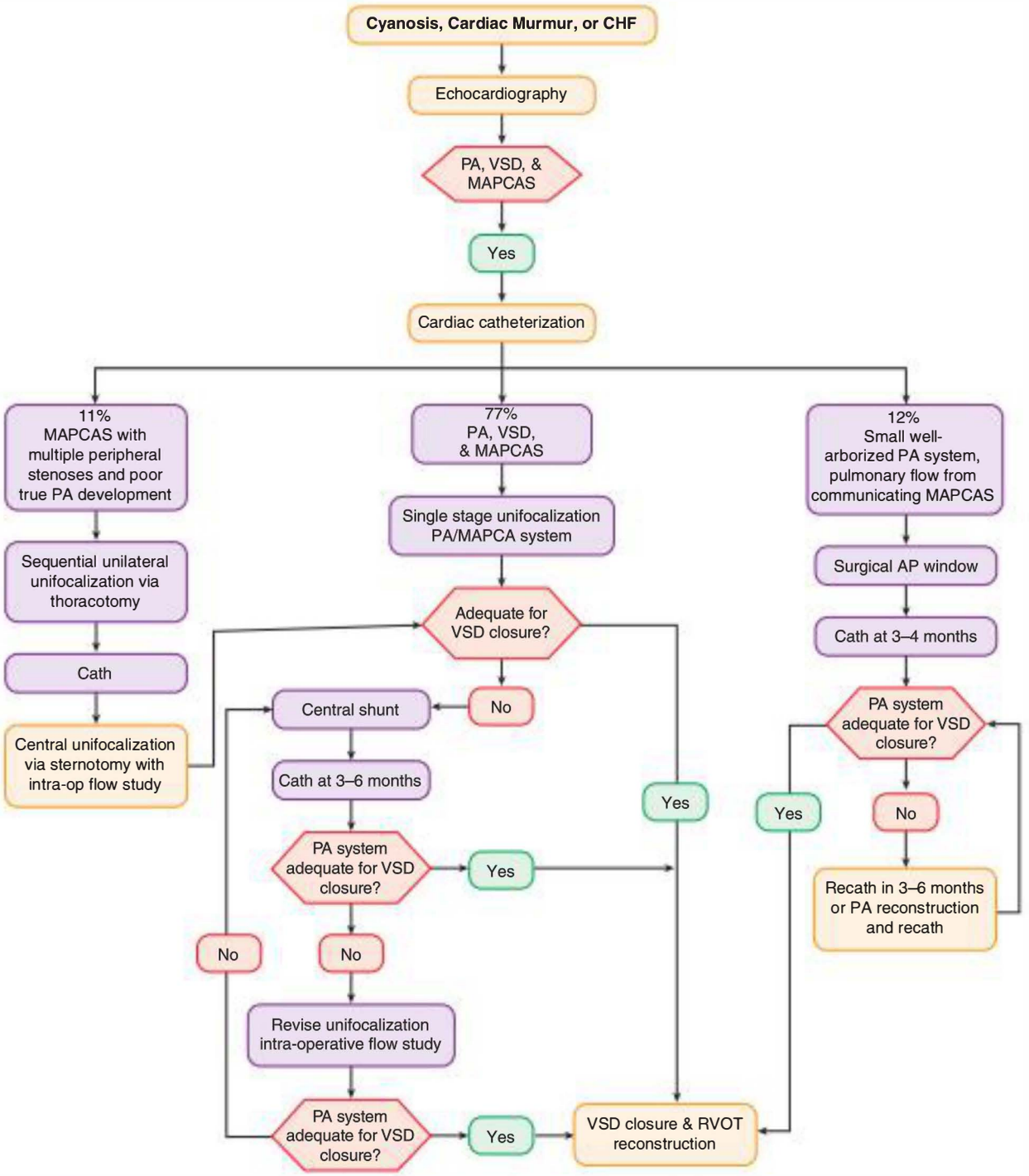



**FIGURE 69-1** Clinical decision-making algorithm in pulmonary atresia with VSD and multiple aortopulmonary collaterals. PA, pulmonary atresia; VSD, ventricular septal defect; MAPCA, major aortopulmonary collateral arteries.

typically normal at birth but will gradually develop evidence of RVH comparable to tetralogy of Fallot. Echocardiography is highly reliable in making the diagnosis of PA, VSD, and MAPCAs, but is typically inadequate for complete evaluation. Echocardiography is sensitive for detection of aortopulmonary collaterals, but inadequate for complete delineation, which is essential for surgical management. The intracardiac anatomy is well delineated by echocardiography. Echocardiography may also show other associated cardiac lesions including ASD or a patent foramen ovale (PFO), multiple VSDs, and coronary anomalies.

Cardiac catheterization is essential in evaluation of the true PAs and aortopulmonary collateral system (Fig. 69-2). It is particularly important to clarify the complete true pulmonary arterial and aortopulmonary collateral distribution. Evaluation of the true PA system may be difficult unless there is duct-dependent pulmonary circulation or a connection between a collateral and the true PA system. Retrograde venous wedge angiography may be needed to evaluate the true PA system in the absence of a ductus or connections between collateral and true PAs. The true central PA system appears as a "seagull"— like vascular structure best visualized in the left lateral or left anterior oblique view. Following intervention, repeated cardiac catheterization is essential to assess results and to plan for subsequent interventions when staged repair is necessary. In addition to imaging, acquisition of hemodynamic data is important. Presence of elevated distal pressure within collateral vessels (mean pressure greater than 20–25 mm Hg) suggests significant PVOD within the affected lung segments. Evaluation of RV pressure may be helpful when planning VSD closure in patients who have been managed by complete unifocalization and placement of an RV–PA conduit without VSD closure, as is advocated by some authors. RV pressure less than 50 percent systemic (under optimal circumstances) or, at most, up to 75 percent systemic suggests that the VSD can be closed. After unifocalization and right ventricular outflow tract (RVOT) reconstruction without VSD closure, the presence of a left-to-right shunt at the ventricular level indicates adequacy of the pulmonary vasculature to tolerate at least one full cardiac output and suitability for VSD repair.

Computed tomographic angiography (CTA) and magnetic resonance imaging are gaining prominence in evaluation of anatomy of complex collaterals in selected circumstances such as in neonates and in older postoperative patients. Due to difficulty in evaluation of angiograms, three-dimensional CTA and MRI reconstructions may be helpful for detailed anatomic assessment and operative planning.

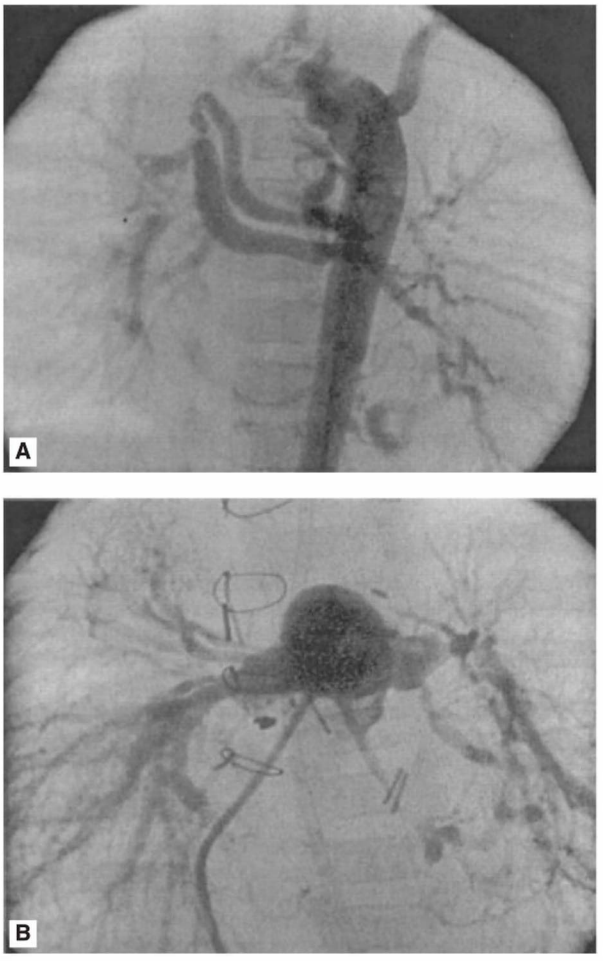



**FIGURE 69-2** Aortic arch angiogram before (**A**) and main pulmonary arteriogram after (**B**) one-stage complete unifocalization in a 2-month-old infant with five MAPCAs and 1.5-mm confluent PAs. VSD was left open. Postoperative angiogram demonstrates complete perfusion of both lungs. (Reproduced with permission from Reddy VM, McElhinney DB, Amin Z, et al. Early and intermediate outcomes after repair of pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries: Experience with 85 patients. *Circulation* 2000;101:1826.)

## GOALS AND PRINCIPLES OF THERAPY

The initial management of patients presenting with PA, VSD, and MAPCAs is based on medical stabilization of the patient so that full evaluation and proper therapeutic planning can be undertaken. Some patients with excessive pulmonary blood flow may require management of CHF. Interventional cardiac catheterization is important in both short- and long-term management. Interventional procedures may include coil occlusion of collaterals providing duplicate flow to individual pulmonary segments and balloon dilatation of stenoses. Pulmonary valve perforation and dilatation may be performed in the very rare instance of PA with VSD and an adequately developed main pulmonary arterial system.

The ultimate goal of surgical therapy is the creation of separated in-series pulmonary and systemic circulations. Ideal age for repair of this lesion is unknown. If the patient is well balanced physiologically, we prefer to perform the repair

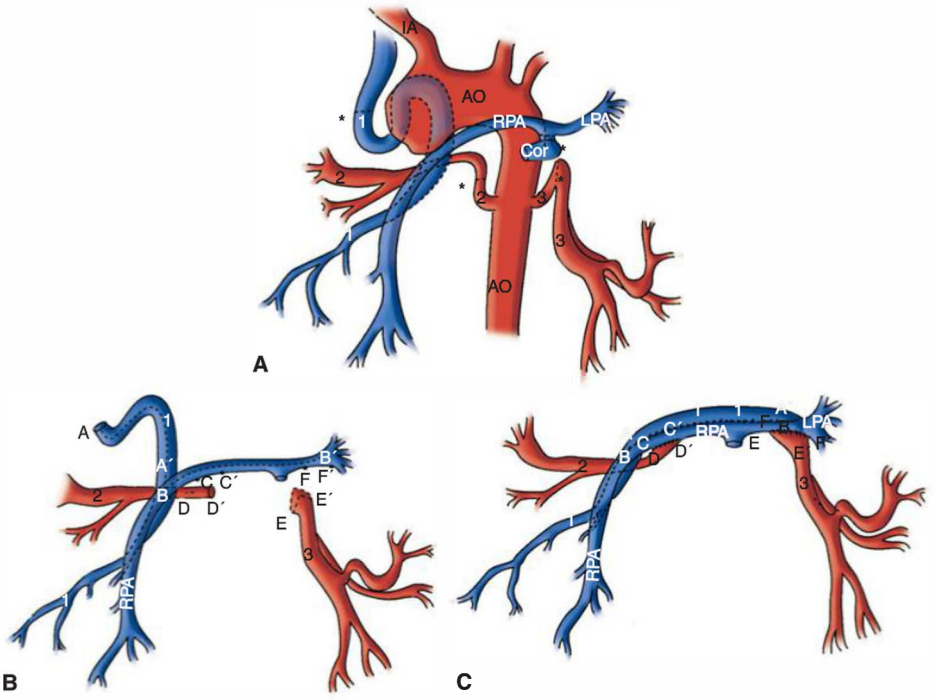



**FIGURE 69-3** Anatomy of pulmonary blood supply and unifocalization in a 3.5-month-old child who underwent one-stage complete unifocalization and repair of tetralogy of Fallot with MAPCAs. **A.** Illustration of pulmonary blood supply with left pulmonary artery (LPa) and right pulmonary artery (RPa), a coronary collateral (COR) connecting to the true pulmonary artery, and three MAPCAs (1–3) from the Innominate artery (IA) and descending aorta (AO). **B.** MAPCAs are opened along the dashed lines A–A′, D–D′, and E–E′, whereas the true pulmonary arteries are filleted open from hilum to hilum (B–B′). **C.** Complete unifocalization and reconstruction of the pulmonary artery is completed with full native tissue continuity. Collateral 1 A–A′ is anastomosed side to side to the incision B–B′ in the true pulmonary artery as a long onlay. Collateral 2 is anastomosed end to side to the undersurface of the RPA from D–D′ to C–C′. Collateral 3 is anastomosed end to side to the undersurface of the LPA from E–E′ to F–F′. (Reproduced with permission from Reddy VM, Liddicoat JR, Hanley FL. Midline one-stage complete unifocalization and repair of pulmonary atresia with ventricular septal defect and major aorto-pulmonary collaterals. *J Thorac Cardiovasc Surg* 1995;109:832–845.)

when the patient is between 3 and 6 months of age, and perform then a single-stage repair. There are many advantages of early one-stage repair. Cardiovascular physiology is normalized and cyanosis is corrected. The patient is protected against pulmonary hypertension related to high flow either through collaterals or through systemic shunts. The number of operations is reduced, reducing the complexity and morbidity of reoperative surgery. The major problem in management is the natural and intervened history of the MAPCAs and the complexity of surgical intervention on the pulmonary vascular bed (Fig. 69-3).

Reconstruction must achieve unobstructed flow from the RV to the PA system. Achieving this goal requires "unifocalization" of the vascular systems, recruiting as much of the true PA- and MAPCA-supplied systems as possible and, eventually, closure of the VSD. The most important physiologic factor indicating favorable ultimate outcome is postrepair RV pressure, which depends on the number of lung segments included in the pulmonary vascular bed and the status of the pulmonary microvasculature. The goal of early intervention is to incorporate as many lung segments in the pulmonary vascular circuit as possible, and to close the VSD; this in turn maximizes the possibility that the pulmonary circulation is exposed to normal pulmonary arterial pressures.

Surgical approaches have included staged reconstruction via thoracotomies with subsequent pulmonary arterial centralization and ultimate VSD closure via sternotomy, staged reconstructions via sternotomies, and single-stage reconstruction.[4–9]

"Single-stage" unifocalization with or without concurrent repair of the VSD is favored by the authors.[10–12] The operation is achievable via sternotomy in most patients, avoiding possible long-term complications of thoracotomy. In patients whose pulmonary arterial system is inadequate to support a full cardiac output due to distal stenosis or hypoplasia unifocalization of the collaterals and creation of a shunt from the ascending aorta to the unifocalized PA system is performed

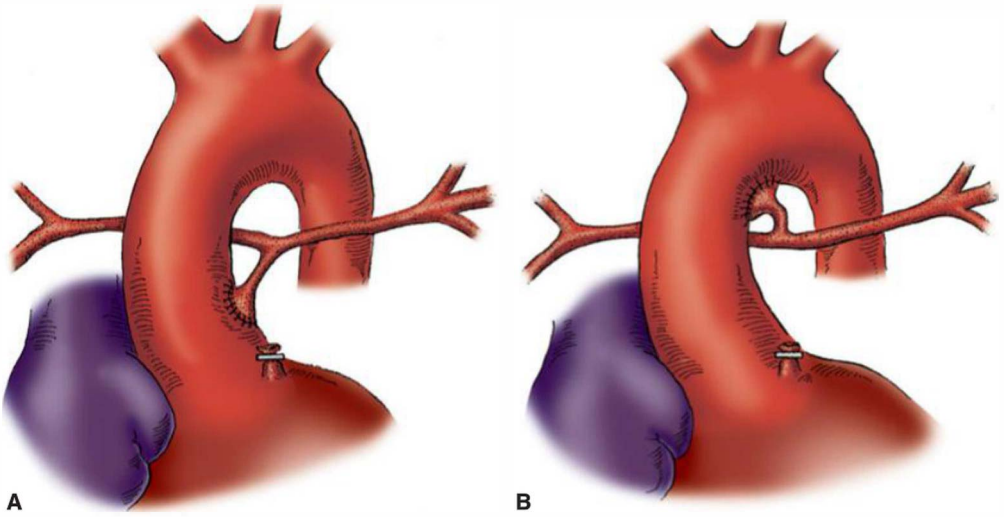



**FIGURE 69-4** Surgical aortopulmonary window. Ideal location for anastomosis varies according to patient-specific anatomic variables and may be dictated not only by pulmonary artery anatomy but also by aortic size and position. **A.** Most common anastomotic position at left posterolateral aspect of ascending aorta, just above sinotubular junction. **B.** Less commonly, the pulmonary artery confluence has better positional lie when located superiorly to the undersurface of the aortic arch. (Reproduced with permission from Rodefeld MD, Reddy VM, Thompson LD, et al. Surgical creation of aortopulmonary window in selected patients with pulmonary atresia and with poorly developed aortopulmonary collaterals a nd hypoplastic pulmonary arteries. *J Thorac Cardiovasc Surg* 2002;123:1147.)

whenever possible. The VSD is left open and early follow-up and reintervention is planned.

In a small minority of patients minute, centrally-confluent true PAs are present with a relatively complete arborization pattern to most or all lung segments. Pulmonary blood flow is, however, from MAPCAs which share dual supply vascular distribution with the true PAs. In these patients, we construct a neonatal "aortopulmonary window" by transecting the main PA close to the infundibulum and anastomosing the small main PA to the ascending aorta to encourage pulmonary vascular growth (Fig. 69-4).[13] Important MAPCAs are ligated. These patients are evaluated for intracardiac repair at 3 to 6 months of age. In a few patients, the majority of MAPCAs have multiple stenoses at the segmental and subsegmental branches. True PAs may or may not be present. This small subgroup of patients with PA, VSD, and MAPCAs are managed by sequential staged thoracotomies.

Patients who have severe cyanosis and inadequate collateralization or a pulmonary vascular bed that is not amenable to reconstruction, or patients who fail unifocalization and complete correction may eventually require pulmonary or heart–lung transplantation. Patients who have had bilateral thoracotomies who require pulmonary transplantation due to failure of unifocalization are very difficult subjects for transplant due to severe cyanosis and development of extensive collateral vessels from the chest wall. Thoracotomy approaches to pulmonary vascular reconstruction are therefore only used when unavoidable.

## SURGICAL THERAPY

The primary objective of surgery is to completely unifocalize the pulmonary arterial and MAPCA complex. Our current approach is to perform first intervention at 3 to 6 months of age (median age of first operation in the authors' series was 8 months). Complete bilateral unifocalization via median sternotomy can usually be achieved (85 percent in the authors' series). Intracardiac repair is achieved as early as possible (56 percent at first operation and 83 percent within 2 years in the authors' series). In patients who are severely cyanotic or over-shunted, earlier intervention is feasible and may be necessary. Customizing the therapeutic approach to the individual patient and creative, meticulous, surgical techniques are essential in achieving good surgical outcomes.

Timing of the VSD closure may be a significant challenge.[14] Patients who have previously undergone PA reconstruction and unifocalization who have demonstrated satisfactory pulmonary vascular growth on follow-up angiography are typically amenable to VSD closure and RV–PA conduit RVOT reconstruction. When there is a question regarding the adequacy of the pulmonary bed to accommodate a full cardiac output, an intraoperative flow study has been used by the authors. When the VSD is closed, a PFO is left to allow for right-to-left shunt in the event of elevated RV pressure in the early postoperative period.

Other authors have advocated using an "adjustable VSD."[15] The VSD is closed with a patch, leaving a deliberate defect in the superior portion of the patch which is encircled with a

purse-string suture. The RVOT is reconstructed, and a pressure-monitoring cannula is placed in the RV. Occlusion of the deliberate "residual" VSD is then attempted. If the VSD can be occluded with resulting RV pressure half or less of the systemic pressure the defect is completely closed. Otherwise the defect is maintained patent to allow for right-to-left shunt. The purse string suture is enclosed in a tourniquet snare and brought to the subcutaneous tissue where it may be easily located and exposed later.

## Operative Technique

The surgical approach to the mediastinum favored by the authors is via a wide midline incision and a median sternotomy. Subtotal thymectomy is performed. The right pleura is widely opened anterior to the phrenic nerve, the right lung is lifted out of the pleural cavity, and the right-sided collaterals are identified and dissected. Similarly, the left pleura is opened and the left-sided collaterals are identified and dissected. Collaterals are rerouted by opening the pleura on both sides posterior to the phrenic nerves. The descending aorta is exposed in the posterior mediastinum and all the collaterals from it are identified, dissected, and controlled. The pericardium is then opened, partial anterior pericardiectomy is performed and the excised portion of pericardium is preserved in glutaraldehyde (0.6 percent). The native PAs, if present, are completely mobilized from hilum to hilum. Any further collaterals from the upper descending aorta are identified and dissected in the subcarinal space between the tracheobronchial angle and the roof of the left atrium by an approach between the right superior vena cava and the aorta. The floor of the pericardial reflection in the transverse sinus is opened and the posterior mediastinal soft tissues are dissected to expose the aortic segment and the collaterals in this region. This is an important maneuver for gaining access to collaterals, which quite often arise from this location (Fig. 69-5). Opening this space also provides the most direct avenue for collateral rerouting for direct tissue-to-tissue anastomosis. In patients in whom collaterals originate from the aortic arch or the neck vessels the vessels are exposed and mobilized. All collaterals are controlled with snares or neurovascular clips before cardiopulmonary bypass is instituted.

As many collaterals as possible are permanently ligated at their origin, mobilized, and unifocalized without cardiopulmonary bypass. When the patient's oxygenation reaches an unacceptably low level, cardiopulmonary bypass is instituted, and the remainder of the collaterals are unifocalized at mild-to-moderate hypothermia with the heart beating. A calcium-supplemented blood prime is used in the cardiopulmonary bypass pump circuit to maintain normal cardiac function. During unifocalization, emphasis is placed on avoiding synthetic or allograft conduits in the periphery and on achieving unifocalization by native tissue-to-tissue anastomosis. Surgical techniques used to achieve native tissue-to-tissue continuity may include side-to-side anastomosis of collaterals to the central PAs (thus augmenting the hypoplastic true PAs),

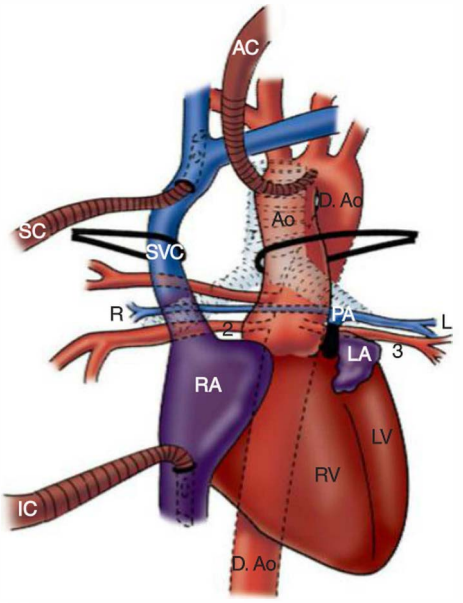



**FIGURE 69-5** The transverse sinus is an important avenue for dissecting, routing, and unifocalizing the collaterals that arise from the descending aorta in the region of the subcarinal space. In this diagram, the MAPCAs are depicted anterior to the tracheobronchial tree. However, collaterals in this region have a variable relation to the extraparenchymal airways and esophagus, and the technique of rerouting and unifocalization must be individualized to optimize the lie of each collateral. Ac, aortic cannula; Ao, ascending aorta; D. Ao, descending aorta; IC, inferior caval cannula; L, left pulmonary artery; LA, left atrium; LV, left ventricle; PA, atretic main pulmonary artery; R, right pulmonary artery; RA, right atrium; RV, right ventricle; SC, superior caval cannula; SVC, superior vena cava. (Reproduced with permission from Reddy VM, Liddicoat JR, Hanley FL. Midline one-stage complete unifocalization and repair of pulmonary atresia with ventricular septal defect and major aorto-pulmonary collaterals. *J Thorac Cardiovasc Surg* 1995;109:832–845.)

side-to-side anastomosis of collateral-to-collateral- or of collateral-to-peripheral true PAs, end-to-side anastomosis of collateral-to-collateral or of collateral-to-true PA, anastomosis of a button of aorta (giving rise to multiple unobstructed collaterals) to the native PAs, end-to-end- or end-to-side anastomosis of collateral-to-central conduit, allograft patch plasty of stenotic distal segments of the collaterals or allograft patch augmentation of the reconstructed neo-central PAs. These anastomoses are achieved directly by bringing collaterals either through the transverse sinus, below the hilum of the lung, or above the hilum to achieve the optimal anatomic result, and by making use of as much of the collateral length as possible. Tension-free tissue-to-tissue anastomosis is essential and collateral length is therefore critically important and consequently given the highest priority. If a discrete stenosis is present in the midportion of a collateral, the collateral is used and the stenosis is managed by side-to-side reconstruction at the stenotic area or, if that is not possible,

by patch augmentation. Collaterals that provide a dual supply to a lung segment together with the true PA supply are unifocalized in order to build up the size of the reconstructed PAs. Particularly difficult aspects of unifocalization may occasionally be completed after aortic cross-clamping and cardioplegic arrest is induced, at moderate hypothermia. If use of patch material is unavoidable we use it noncircumferentially so that the growth potential of the native tissue is preserved. We limit the use of circumferential nonviable conduits to the central mediastinum. Essential concepts necessary to achieve this type of unifocalization are flexibility regarding reconstruction, aggressive mobilization, maximizing the length of the MAPCAs and creative rerouting.

In a total of over 1500 unifocalized collaterals in our experience, only a small number have been reconstructed with circumferential nonviable conduit (expanded polytetrafluoroethylene). In patients with absent or string-like true PAs, a non-valved allograft conduit may sometimes be necessary to reconstruct the central left and right PAs. In such patients, in whom growth potential is an issue, the hilar regions are reconstructed only with native tissue (using the techniques described) and the conduit serves as the main left and right PAs with the graft limited to the pericardial cavity.

Following completion of the unifocalization (when indicated) the VSD is closed. Suitability for closure of the VSD may be determined by preoperative studies, or may require an intraoperative flow study to assess the total resistance of the pulmonary vascular bed. The flow study is performed while on cardiopulmonary bypass. The recreated main PA supplying the entire pulmonary vascular bed is cannulated and perfused using a calibrated pump head from the cardiopulmonary bypass pump. Flow from the pump head is progressively increased up to the equivalent of at least one cardiac output. A pressure catheter is placed in the PA system, and the left atrium is vented. If the mean PA pressure is less than 25 mm Hg, the VSD can be closed. If the mean pulmonary pressure is greater than 25 mm Hg a central shunt or a restrictive right-ventricle-to- PA conduit is created.

If VSD closure is indicated, a longitudinal ventriculotomy is made in the RV infundibulum and hypertrophied muscle bundles are resected. The VSD is closed with a glutaraldehyde-fixed autologous pericardial patch or a polyester (Dacron) patch. The right atrium is opened to inspect the atrial septum. An atrial septal defect or PFO, if present, is closed leaving a small unidirectional interatrial communication as a "pop-off" valve for right-to-left shunt of venous blood in case of postoperative RV dysfunction. In occasional cases with an intact atrial septum a small one-way interatrial communication is created. A homograft-valved conduit is tailored and used to connect the RV to the reconstructed neopulmonary arterial system. A valved bovine jugular vein conduit (Contegra®) may provide a useful alternative.[16] The distal conduit is anastomosed to the reconstructed PAs using a 6-0 or 7-0 monofilament nonabsorbable suture. The distal anastomosis may be performed prior to cardioplegic arrest in order to minimize ischemic time when the decision has been made to close the VSD. If needed, a distal extension of the conduit tissue can be shaped to augment the reconstructed central branch PAs. The proximal RV-to-conduit anastomosis is made with a continuous monofilament nonabsorbable suture by directly anastomosing the conduit around a portion of its circumference, and augmenting the anastomosis with a "hood" of either pericardium or homograft tissue to complete the anastomosis. The proximal anastomosis may be made after removal of the aortic cross-clamp and reperfusion of the heart during the rewarming period. A pressure-monitoring catheter is placed into the PAs across the RVOT. Following adequate rewarming, the patient is weaned from cardiopulmonary bypass with constant monitoring of the systemic arterial pressure, pulmonary arterial pressure, and atrial pressures. After separation from bypass, these pressures are measured continuously and transesophageal echocardiography is performed to ensure that there are no significant residual defects.

Bilateral pleural and mediastinal drains are placed and the sternum is closed. If bleeding or ventilation is a significant concern, we electively leave the sternum open and close the chest incision with a siliconized rubber (Silastic®) patch. Secondary sternal closure is performed on the second or third postoperative day once the patient is physiologically stable.

## POSTOPERATIVE MANAGEMENT

Postoperatively patients are ventilated, kept well sedated and, if necessary, pharmacologically paralyzed until hemodynamically stable and on minimal ventilatory support. Inotropic support is provided using dopamine, milrinone, calcium chloride, and epinephrine infusions as needed. Important postoperative problems include pulmonary parenchymal reperfusion injury, pulmonary hemorrhage, bronchospasm, and phrenic nerve injury. Reperfusion injury most typically occurs in pulmonary segments that are severely hypoperfused preoperatively. Bronchospasm may occur due to extensive hilar and intraparenchymal dissection. Phrenic nerve injury is uncommon and can be avoided by meticulous attention during dissection. Splanchnic organ dysfunction has previously been described and was a problem in the early experience of the authors. The problem typically presents as acute hepatic dysfunction or, rarely, intestinal necrosis. It is now not common; maintaining perfusion pressure over 40 mm Hg during cardiopulmonary bypass appears to have been significantly contributory in resolving the problem.

### Postoperative Follow-up and Evaluation

After repair all patients are closely followed clinically. Routine echocardiography and nuclear pulmonary flow scans are performed at least every 3 months. In patients in

whom the VSD is left open or a shunt is made to the unifocalized pulmonary arterial system, a cardiac catheterization is performed approximately 3 months postoperatively. If the $Q_p/Q_s$ ratio is over 2:1 the VSD is closed. If less than 2:1 the pulmonary arterial system is assessed for stenotic lesions that may be amenable to percutaneous catheter based or surgical intervention. Following VSD closure, the status of the conduit and of the peripheral PAs are closely followed by serial clinical and echocardiographic evaluation in order to evaluate for stenosis or insufficiency. Cardiac catheterization is performed electively approximately 1 year following complete repair.

## CURRENT OUTCOMES

Reddy et al. reported 85 patients with PA, VSD, and MAPCAs.[12] Fifty-six underwent complete one-stage unifocalization and intracardiac repair. In 23 patients the VSD was left open at the time of complete unifocalization. There were six early deaths and seven late deaths. Actuarial 3-year survival was 80 percent.

Rodefeld et al.[13] reported on patients with diminutive PAs who require creation of an aortopulmonary window. In the series of 18 patients with confluent diminutive PAs who underwent the procedure there was 100 percent early survival and 2 late deaths unrelated to the procedure. Follow-up angiography demonstrated excellent development of the true PAs.

Hanley et al. have now accumulated data on 462 patients with VSD and MAPCAs who were managed as described.[17] The cohort includes the patients previously described by Reddy et al. Median age at first surgery was 7.7 months. Initial operation was complete unifocalization via median sternotomy in 76 percent. Intracardiac repair was achieved at initial operation in 56 percent,. Ninety percent of patients were completely repaired at 5 years. Operative mortality for the most recent 9 years was 2.3 percent. Mortality for the entire series was 5.9 percent, with actuarial survival at 5 years of 85.5 percent. Surgical reintervention for PA reconstruction was required in 22.6 percent of patients.

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## PULMONARY ATRESIA WITH VENTRICULAR SEPTAL DEFECT AND MAJOR AORTOPULMONARY COLLATERALS BOARD REVIEW QUESTIONS (CHAPTER 69)

1. Which is correct regarding anatomy of pulmonary atresia with ventricular septal defect and major aortopulmonary collaterals (PA–VSD with MAPCAs)?
   A. A large central confluence of the main PAs is usually present.
   B. The MAPCAs probably originate from the splanchnic vessels.
   C. Most MAPCAs originate from the distal descending thoracic aorta.
   D. The VSD is typically posteriorly malaligned.
   E. The defect is not associated with the VATER syndrome.

2. Which is a correct clinical presentation of PA–VSD with MAPCAs?
   A. Over 80 percent are symptomatic at birth
   B. The VSD is usually restrictive
   C. Patients with extensive collaterals may have minimal symptoms
   D. Cyanosis is caused solely by pulmonary microvascular obstructive disease
   E. Cyanotic spells are due to RV infundibular spasm

3. Which is not required during cardiac catheterization for preoperative evaluation of PA–VSD with MAPCAs?
   A. Delineation of true PA anatomy
   B. RV pressures
   C. Assessment of collateral distribution
   D. Venous wedge angiography
   E. Selective coronary angiography

4. Which is correct regarding surgical technique for repair of PA–VSD with MAPCAs?
   A. Collaterals are rerouted by opening the pleurae anterior to the phrenic nerves.
   B. The native PAs should not be mobilized.
   C. Opening the floor of the pericardial reflection in the transverse sinus provides the most direct avenue for collateral rerouting.
   D. Collaterals should be controlled after instituting cardiopulmonary bypass.
   E. The majority of the collaterals are unifocalized after cross-clamping.

5. Which of the following is true for outcomes after surgical repair of PA–VSD with MAPCAs?
   A. Early mortality is 50 percent in patients requiring creation of an aortopulmonary window.
   B. About 75 percent of patients can undergo complete unifocalization at the initial operation.
   C. Intracardiac repair is achieved in less than 30 percent.
   D. Overall operative mortality is 10 to 15 percent.
   E. Surgical reintervention for PA reconstruction is required in less than 10 percent.

## ANSWERS

1. **Answer: B.** The MAPCAs probably originate from the splanchnic vessels. A small central confluence is usually present, and most of the MAPCAs originate from the proximal descending thoracic aorta. The VSD is typically anteriorly malaligned. The defect is associated with the VATER, Alagille, DiGeorge, and trisomy 21 syndromes.
2. **Answer: C.** Patients with extensive collaterals may have minimal symptoms. About 80 percent of patients have minimal symptoms and mild cyanosis. The VSD is usually unrestrictive. Cyanosis may be caused by pulmonary microvascular obstructive disease, inadequate collaterals, or collateral stenosis. Cyanotic spells are caused by decreases in systemic vascular resistance that result in markedly decreased pulmonary blood flow.
3. **Answer: E.** Selective coronary angiography is not necessary for evaluation of these patients. Delineation of both true PA and collateral anatomy is critical, with retrograde venous wedge angiography used in patients without connections between the collaterals and the true PAs. Assessment of RV pressures helps plan VSD closure strategy.
4. **Answer: C.** Opening the floor of the pericardial reflection in the transverse sinus provides the most direct avenue for collateral rerouting. Collaterals can also be rerouted by opening the pleurae posterior to the phrenic nerves. The native PAs should be extensively mobilized. Collaterals should be controlled prior to instituting cardiopulmonary bypass, and as many as possible should be unifocalized without cardiopulmonary bypass.
5. **Answer: B.** About 75 percent of patients can undergo complete unifocalization at the initial operation. All patients requiring creation of an aortopulmonary window survived the operation. Intracardiac repair is achieved in over 50 percent of patients at the initial operation. Overall current operative mortality is approximately 5 percent. Surgical reintervention for PA reconstruction is required in about 20 percent of patients.

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# Pulmonary Stenosis and Pulmonary Atresia with Intact Ventricular Septum

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**KEY CONCEPTS**

- Pulmonary stenosis
  - Right ventricular outflow tract (RVOT) obstruction at the level of the pulmonary valve
  - Pulmonary annulus may be stenotic or normal.
  - Treatment is often with balloon valvotomy versus surgical valvotomy.
  - Recurrent stenosis and insufficiency is common with surgical or balloon valvotomy.
- Pulmonary atresia (PA) with intact ventricular septum (IVS)
  - Complex defect with complete absence of communication between right ventricle (RV) and pulmonary arteries
  - Characterized by varying degrees of RV and tricuspid valve hypoplasia
  - Multiple surgical interventions common in childhood
  - Surgical treatment strategies based on size and development of RV and tricuspid valve

## INTRODUCTION

**Pulmonary stenosis** (PS) at the valvar level accounts for 8 to 10 percent of all congenital heart defects. In most patients, the pulmonary valve is found to be dome-shaped, with commissural fusion and variable subvalvar right ventricular outflow tract (RVOT) obstruction. The pulmonary annulus may be normal in size or smaller than predicted, and a patent foramen ovale (PFO) or atrial septal defect (ASD) is usually present. Clinical presentation is variable. Although severe PS may present in the newborn period, most of these lesions do not manifest significant signs and symptoms until later in childhood. Clinical findings are directly related to the severity of the RVOT obstruction and the degree of shunting across the atrial septum. Timing of intervention is based on severity of clinical findings and is indicated when an RVOT gradient exceeds a mean of 50 mm Hg. Although balloon valvotomy has become the initial therapeutic intervention in most patients, surgical valvotomy still remains an important form of intervention in a subset of these patients. Both catheterization with balloon valvotomy and surgical valvotomy are associated with low morbidity and mortality and excellent long-term survival.

**Pulmonary atresia (PA) with intact interventricular septum (IVS)** is an uncommon defect, representing between 1 and 3 percent of all congenital heart lesions. By definition, there is no communication between the right ventricle (RV) and the pulmonary arteries and no antegrade pulmonary blood flow through the RVOT. Consequently, a patent ductus arteriosus (PDA) is essential for early survival. The defect presents with varying degrees of hypoplasia of the RV and tricuspid valve, and often involves RV-to-coronary artery fistulas (45 percent). In addition, the tricuspid valve may have an Ebstein malformation (10 percent), and a right ventricle-dependent coronary circulation (RVDCC) is found in 10 to 15 percent of patients.

In neonates with PA/IVS, surgical classification of RV hypoplasia into mild (more than two-thirds of normal), moderate (one-third to two-thirds of normal), and severe (less than one-third of normal), as well as accurate assessment of the TV annular diameter, is useful in directing surgical management. A similar classification strategy is used for surgical management in older children. This allows patients to be stratified into those who will most likely achieve a biventricular repair and those who are best suited for a single ventricle pathway.

# PULMONARY STENOSIS

## Definition

PS with IVS is characterized by RVOT obstruction at the level of the pulmonary valve. The pulmonary valve is typically dome-shaped, with commissural fusion of the leaflets and a small central orifice. The pulmonary annulus may be either normal in size or smaller than predicted by the patient's weight. The RV is usually of normal size and morphology but may develop RV hypertrophy very early in life. This progression of RV hypertrophy may lead to further obstruction of the RVOT at the infundibular level.

## Historical Note

The initial pathologic description of PS is credited to Morgagni in 1761. The first attempt at surgical treatment of this lesion is attributed to Doyen in 1913. In his report, Doyen described a transventricular valvotomy using a tenotomy knife with an unsuccessful outcome.[1] In 1948, Sellors and Brock reported successful blunt valve dilatation using a transventricular approach.[2] Several successful cases of open pulmonary valvotomy using systemic hypothermia and ventricular fibrillation also followed. Open pulmonary valvotomy with the use of cardiopulmonary bypass was successfully introduced in 1955. This remained the primary treatment for patients with PS until the technique of balloon valvotomy was introduced by Semb and associates in 1979. In 1982, Kan and associates at the Johns Hopkins Hospital first reported successful percutaneous balloon valvotomy in a patient with PS.[3] Balloon valvotomy has since become the mainstay of initial therapy for PS and has succeeded surgical therapy as a primary intervention in most patients.

## Epidemiology

Obstructive lesions of the RVOT are found in 25 to 30 percent of children with congenital heart disease. Isolated PS at the level of the pulmonary valve with an intact IVS accounts for approximately 8 to 10 percent of all congenital heart defects, with a slightly higher incidence in females. Without intervention, the onset of hypoxia and heart failure in neonates carries an extremely high mortality. There is a reported increased incidence of 2 to 4 percent in siblings of patients with this particular defect.

## Etiology and Pathogenesis

The etiology of this lesion is unknown. Failure of the pulmonary valve leaflets to form and separate adequately during embryonic development results in limited mobility and stenosis of the valve. The consequent turbulence of blood flow across this region during subsequent growth and development leads to dysplasia and fibrous distortion of the valve leaflets and further increases the degree of stenosis. RV hypertrophy develops secondarily and is directly related to the severity of the obstruction. Rarely, neonates may present with enlarged RVs and cardiomyopathy, associated with a very poor prognosis despite early intervention.

## Clinical Features

Neonates who present with critical PS in the newborn period develop severe cyanosis and congestive heart failure. The clinical findings are directly related to the severity of the stenosis as well as to the degree of right-to-left shunting across the interatrial septum. On physical examination, most children with PS present with a harsh holosystolic ejection murmur, an ejection click, and a palpable thrill over the pulmonic valve region. These neonates often appear irritable, tachypneic, and cyanotic due to shunting at the atrial level. Although severe PS may present in the newborn period, most of these lesions do not manifest significant clinical findings until later in childhood. The timing of intervention is usually determined by the severity of clinical findings and is indicated for a documented mean gradient of 50 mm Hg or greater across the RVOT. The results of treatment and long-term outcomes are directly related to the size of the RV and the patient's age at presentation.

## Laboratory and Diagnostic Features

In patients with PS, an electrocardiogram typically reveals right-axis deviation, prominent P waves, and RV hypertrophy. On the chest radiograph, prominent pulmonary artery (PA) shadows secondary to poststenotic dilatation may be observed. The cardiac shadow is usually normal except in severe cases with associated congestive heart failure. Transthoracic echocardiographic examination establishes the severity of the stenosis, the gradient across the RVOT, and the size of the ASD. Cardiac catheterization is performed to obtain additional diagnostic information, and in many patients to perform therapeutic intervention with a balloon valvotomy.

## Differential Diagnosis

The differential diagnosis includes all congenital heart defects that have RVOT obstruction as an anatomic finding. They include defects such as tetralogy of Fallot, PS with ventricular septal defect (VSD), PA/IVS, and all morphologic cardiac abnormalities characterized by infundibular obstruction. Echocardiography can easily delineate these defects in most patients and identify those with isolated PS with an IVS.

## Therapy

The medical management of these patients is similar to that for any neonate or child with RVOT obstruction. In the neonate with severe PS and cyanosis, ductal patency must be

maintained with prostaglandin infusion, and pulmonary vascular resistance must be reduced to ensure adequate pulmonary blood flow. Systemic hypotension is avoided as it may result in reduced ductal flow to the pulmonary arteries and lead to increased hypoxemia. These patients may also have dynamic obstruction in the infundibular region secondary to RV myocardial hypertrophy. Inotropic agents must therefore be used with caution as increased contractility may, in turn, worsen functional obstruction across the RVOT. This will result in further compromise of pulmonary blood flow. After initial stabilization, percutaneous intervention with balloon valvotomy is often performed. If this is unsuccessful in relieving the obstruction, surgical valvotomy can be then performed as either an open technique using cardiopulmonary bypass or with a transventricular approach using a dilator without bypass.

### OPERATIVE PROCEDURES

***Open Pulmonary Valvotomy Using Cardiopulmonary Bypass.*** Open pulmonary valvotomy is performed through a median sternotomy using cardiopulmonary bypass and bicaval cannulation. If present, the PDA is ligated or snared prior to the initiation of cardiopulmonary bypass. An aortic cross clamp is applied, and antegrade cardioplegia is administered through the aortic root to achieve myocardial arrest. If no ASD is present, cardioplegic arrest may be omitted and the procedure performed with the heart beating. Otherwise, the PFO or ASD is closed through a right atriotomy, either with primary suture closure or with a patch of autologous pericardium. A vertical pulmonary arteriotomy is then performed on the anterior wall of the main PA and extended down to the level of the pulmonary valve. The stenotic valve is inspected, and the fused commissures are carefully identified and incised with a No. 11 scalpel or fine vascular scissors. The incisions in the valve tissue should extend to the edge of the annulus (Fig. 70-1). Any valvular adhesions to the PA wall are sharply incised. A partial valvectomy may be necessary to remove thickened valve tissue or dense fibrous scarring on dysplastic leaflets. The infundibulum is then inspected through the valve for any subvalvular stenosis, and sharp infundibular resection may be performed if necessary. A dilator may be used to size the valve annulus and dilate the annular tissue. A transannular patch may be required if the annulus is small. The arteriotomy may be closed primarily or with a patch of autologous or bovine pericardium to reduce the risk of any residual obstruction.

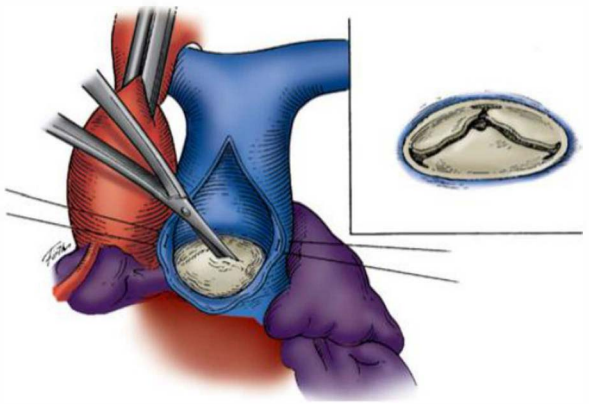


**FIGURE 70-1** Open pulmonary valvotomy using cardiopulmonary bypass. The pulmonary valve is approached through a vertical arteriotomy and the fused commissures are incised with a No. 11 scalpel or fine scissors.

***Off-Pump Transventricular Pulmonary Valvotomy.*** If no ASD is present, a pulmonary valvotomy may be performed through a median sternotomy using an off-pump transventricular technique. A purse-string suture is placed in the anterior wall of the RV. An angiocatheter connected to a pressure transducer is first introduced through the purse-string suture into the RV and then into the PA. Using the same technique, progressively larger metal dilators are then introduced through the RV wall and across the valve membrane. If the valve does not dilate easily, a long vascular clamp can be used to initially disrupt the valvar tissue. After adequate dilation is achieved, the purse string is tied and reinforced. If adequate relief of obstruction is not achieved, then open valvotomy may be performed with cardiopulmonary bypass, while a systemic-to-pulmonary shunt may be added to augment pulmonary flow for persistent cyanosis.

## Results

Most patients with PS are operated on electively and require routine pre- and postoperative care. In neonates, the management of acidosis, electrolyte derangements, and congestive heart failure should be aggressively pursued prior to surgery. Following surgical correction, there is often a residual gradient across the RVOT. Inotropic support should be used cautiously in the postoperative phase in order to avoid exacerbation of any residual infundibular obstruction. Mild and moderate residual gradients often resolve with age and the patient's growth.

Both balloon valvotomy and surgical valvotomy are associated with low morbidity and mortality rates and excellent long-term survival. Each has a significant incidence of recurrent stenosis, requiring additional early or late intervention. There is also a significant incidence of pulmonary valve insufficiency following both procedures. Mild-to-moderate pulmonary insufficiency is tolerated remarkably well by most patients, and its long-term clinical importance is a current topic of investigation. Although early mortality is not reportedly increased in patients with significant pulmonary insufficiency, the development of RV enlargement, RV dysrhythmias, and abnormal RV response to exercise may lead to increased long-term morbidity and mortality in these patients. Although overall survival following surgical treatment of isolated PS remains excellent, many patients undergo late reintervention after 30 years of follow-up.[4]

Therefore, these patients should be followed in the long term for the need of possible late reintervention or pulmonary valve replacement.

A multi-institutional study by Hanley and associates reported a 30-day survival of 89 percent and a 4-year survival of 81 percent for all modes of intervention in neonates with critical PS.[5] Of note, 26 percent of these patients required reintervention within 2 years for residual stenosis (defined as a gradient greater than or equal to 30 mm Hg). Following successful pulmonary valvotomy (after either initial intervention or reintervention), RV size approaches normal in more than 90 percent of these patients.

A report by Rao and associates on 80 patients treated initially with balloon valvotomy with follow-up between 3 and 10 years showed a freedom from repeat balloon valvotomy or surgery of 88 and 84 percent at 5 and 10 years, respectively.[6] Furthermore, surgical reintervention in older children is associated with minimal morbidity and mortality and excellent short- and long-term outcomes.

## PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM

### Definition

PA/IVS is a congenital defect characterized by lack of communication between the RV and pulmonary arteries (PAs), resulting in no antegrade blood flow from the RVOT to the pulmonary arteries. A PDA is essential for maintaining adequate pulmonary blood flow and for early survival. Unlike PA with VSD, aortopulmonary collateral arteries are rarely found in patients with PA/IVS. The defect presents with varying degrees of hypoplasia of the RV and tricuspid valve and often involves fistulas from the RV cavity to the coronary arteries. Morphologically and functionally, the hypoplastic tricuspid valve usually varies in direct correlation with the size of the RV chamber. Coronary artery fistulas are present in up to 45 percent of cases and are more common in patients with severely hypoplastic RVs and small but competent tricuspid valves.[7] In addition, it should be noted that an Ebstein's malformation of the tricuspid valve might be present in 10 percent of cases.[8] These patients may present with marked cardiomegaly due to right atrial (RA) enlargement, severe tricuspid regurgitation, and a relatively large RV size.

### Historical Note

Surgical treatment of this PA/IVS was historically associated with very high morbidity and mortality. The low incidence of this defect combined with its extreme morphologic variability delayed the development of a standardized approach to surgical therapy.

The original Greenwold classification[9] of PA/IVS described this defect by two types of RVs: Type I with a hypoplastic RV and Type II with a normal or dilated RV. A further refinement of this classification was offered by Goor and Lillihei who described the tripartite morphology of the RV (a sinus inlet part, a trabecular part, and a conus or outlet portion) and used this as a basis for surgical therapy.[10] Bull and associates introduced as part of the pre- and intraoperative decision-making process the actual annular diameter of the tricuspid valve.[11] More recently, the surgical approach to PA/IVS has been based on a quantitative *Z*-score assessment of the tricuspid valve diameter.[12] The *Z*-score is determined by comparing the estimated diameter of the tricuspid valve (as measured by echocardiography) to the expected "normal" size and calculating the difference of the two values in standard deviations. In 1989, Billingsley and associates from UCLA introduced a surgically oriented classification of mild, moderate, and severe hypoplasia of the RV that is used today by many centers.[13]

Current surgical approaches to patients with PA/IVS are primarily based on the degree of RV hypoplasia and the degree of TV hypoplasia. In most patients, the degree of hypoplasia of these two structures correlate quite well and this facilitates the classification of these patients for purposes of surgical management. With a more systematic approach to this defect, increasing surgical experience, and improved diagnostic modalities, long-term outcomes have steadily improved.[14,7,15]

### Epidemiology

In contrast to other forms of RVOT obstruction, PA/IVS is an uncommon congenital cardiac malformation, representing between 1 and 3 percent of all congenital heart defects.[16] Without early surgical intervention, children with PA/IVS have an extremely high mortality rate. The natural history in untreated patients is a 50 percent mortality rate at 2 weeks of life and a mortality of approximately 85 percent at 6 months.[17] Death occurs as a consequence of severe hypoxemia and progressive metabolic acidosis secondary to closure of the ductus arteriosus and subsequent loss of pulmonary blood flow. In general, most children with PA/IVS will require multiple surgical interventions beginning in the neonatal period and continuing to one or more interventions later in life.

### Etiology and Pathogenesis

The etiology of this defect remains unknown. A failure of formation of a patent pulmonary valve during embryonic development results in a completely obstructed RVOT. The obstruction varies in form and may be a relatively thin tissue membrane at the end of a well-formed infundibulum or a thick muscular wall with a poorly formed, or absent outflow tract. Since the ventricular septum remains intact, forward blood flow through the RV is precluded. The growth and development of the RV and tricuspid valve (TV) in utero are severely compromised by this lack of forward flow. Both structures tend to follow a similar pattern of hypoplasia,

which is reflected by the TV annular size and the reduced size and volume of the RV chamber. RV-to-coronary artery fistulas are present in 45 percent of cases and are more common in those patients with a severely hypoplastic RV and a small competent TV.[13] In 10 percent of patients, the coronary circulation may be dependent on RV pressure for perfusion by way of fistulous communications associated with severe proximal coronary artery stenosis. Pulmonary blood flow in the neonate is dependent almost entirely on a PDA, as aortopulmonary collaterals are uncommon with this defect. Ebstein's malformation of the TV is seen in 10 percent of patients, adding significantly to the severity of the defect. Although no specific genetic pattern of inheritance has been identified, PA/IVS has been reported in siblings and associated with trisomy 18 or 21.[8]

## Clinical Features

Although prenatal diagnosis is increasing for this defect, most neonates with PA/IVS are still diagnosed shortly after birth. The diagnosis is often prompted by varying degrees of hypoxia and cyanosis within the first week of life. Physical examination is often remarkable for prominent venous pulsations. A significant systolic murmur may be indicative of tricuspid regurgitation. This must be differentiated from the continuous machinery murmur of a PDA. Prostaglandin $E_1$ ($PGE_1$) therapy should be initiated as early as possible to maintain ductal patency. Neonates with hypoxia and poor perfusion in spite of medical management should be evaluated for the presence of a restrictive ASD. In this case, balloon septostomy should be performed urgently to relieve the obstruction at the atrial level. Neonates with severely hypoplastic RVs may also require open atrial septostomy. Classification of the defect is determined by echocardiography. Cardiac catheterization and an appropriate operative procedure are selected based on assessment of RV morphology, TV size, the development of the RVOT, and the coronary circulation.

## Laboratory and Diagnostic Features

In neonates with PA/IVS, an electrocardiogram usually shows progressive evidence of RA enlargement with prominent P waves. The pattern of RV hypertrophy that is present in most neonates is absent. A chest radiograph is usually unremarkable at birth but may later reveal an increased heart shadow secondary to RA and left ventricular (LV) enlargement. The lung fields are usually clear with normal to diminished vascular markings. Echocardiography remains the initial diagnostic study to identify the anatomic abnormalities and assess RV morphology. The size of the ventricular cavity, valve dimensions and function, and the nature of the RVOT obstruction are also evaluated. Because of the complexity and morphologic variability of PA/IVS, the anomaly must be defined by both echocardiography and right/left heart catheterization. Catheterization should determine the size and competency of the TV, the degree of RV hypoplasia, the size of the pulmonary arteries, the coronary anatomy and presence of coronary sinusoids and fistulas, and ventricular function. Selective coronary injections and an injection into the RV are also required for a complete evaluation. RV-to-coronary artery fistulas are frequently accompanied by the development of fibrous intimal hyperplasia, resulting in stenosis or complete obstruction of the native coronary circulation. The presence of obstructive lesions in the proximal coronaries may produce a RVDCC. Such patients are at high risk for myocardial ischemia as desaturated blood from the RV perfuses a significant portion of the myocardium. An even greater risk of myocardial ischemia is incurred by the reduction of diastolic aortic pressure resulting from the creation of a systemic-to-PA shunt. In such patients, decompression of the RV by either an outflow tract patch or a pulmonary or tricuspid valvotomy is poorly tolerated and may lead to acute myocardial infarction and intraoperative demise. The presence or absence of a RVDCC by catheterization must be established in a neonate prior to determining the operative strategy.

## Differential Diagnosis

The differential diagnosis encompasses all congenital heart defects with PA. This includes such defects as PA with VSD and single-ventricle defects associated with PA. Echocardiography can easily delineate these defects in most patients and correctly identify those with isolated PA/IVS. Cardiac catheterization is performed in almost all neonates with PA/IVS to confirm the diagnosis and to define and evaluate the anatomy.

## Therapy

Previous surgical experience has indicated that the surgical management of patients with PA/IVS should be based primarily on an anatomic classification system that specifically defines the degree of RV hypoplasia and the TV annular size. A variety of surgical strategies has been proposed in the past for the treatment of these infants.[18–23] We and others have found classification of the RV hypoplasia to be an accurate and consistent approach to surgical therapy.[24,7,25–27] Using this approach, neonates with PA/IVS are initially separated into three groups of mild, moderate, and severe RV hypoplasia.

In patients with mild RV hypoplasia, the TV and RV cavity are approximately two-thirds or greater of the calculated normal size and the RVOT is well developed. This usually correlates with a *Z*-score for the TV between 0 and –2. In patients with moderate RV hypoplasia, the TV and the RV cavity are approximately one-half of calculated normal size (with a range of one-third to two-thirds of normal) and the pulmonary outflow tract is usually developed enough to perform an effective pulmonary valvotomy. This usually

correlates with a *Z*-score for the TV of −2 to −4. In patients with severe RV hypoplasia, the TV and RV cavity are one-third or less of calculated normal size and the pulmonary outflow tract is not amenable to an effective pulmonary valvotomy. This usually correlates with a *Z*-score for the TV of −4 to −6. This approach is not based on any single anatomic component such as RV volumes or the size of the tricuspid annulus but instead assesses the overall RV morphology and the degree of both TV and RV hypoplasia.

During the initial evaluation of patients with PA/IVS, special attention must be paid to the anatomy of the coronary circulation. Abnormalities of the coronary circulation are often found in the severely hypoplastic group and dictate which surgical management options are indicated.[28,14] During fetal development, RV hypertension may cause intramyocardial sinusoids to develop. These sinusoids may branch extensively into blind channels or communicate by fistulas with the coronary artery circulation. The morphology of these sinusoids and their specific communications are extremely variable and can change over time. Proximal coronary artery stenoses or obstructions may develop in a coronary artery supplied by these intramyocardial sinusoids. If the distal coronary artery flow is dependent on these sinusoids for adequate myocardial perfusion, they are termed RVDCC.[29] Decompression of the RV in these patients is contraindicated and may lead to acute myocardial ischemia and death. The preferred management strategy for these patients is single-ventricle palliation to a Fontan procedure.[30]

**TABLE 70-1: Surgical Management of Pulmonary Atresia with Intact Ventricular Septum in Neonates**

| Classification of RV Hypoplasia | RV Morphology | Treatment |
|---|---|---|
| Mild | RV cavity more than two-thirds normal size<br>TV *Z*-score 0 to −2<br>Well-developed RVOT | Pulmonary valvotomy with transannular patch and shunt or valvotomy only |
| Moderate | RV cavity one-third to two-thirds normal size<br>TV *Z*-score −2 to −4<br>Moderately hypoplastic RVOT | Pulmonary valvotomy with transannular patch and shunt |
| Severe | RV cavity less than one-third normal size<br>TV *Z*-score −4 to −6<br>Severely hypoplastic or absent RVOT | Shunt only or shunt and tricuspid valvotomy |

## SURGICAL MANAGEMENT OF NEONATES

Almost all neonates with PA/IVS will require surgical intervention early in life in order to survive. Treatment with $PGE_1$ maintains pulmonary flow through the PDA and allows time for medical stabilization, diagnostic evaluation, and surgical decision-making. Once the anatomy and morphology of the defect is defined by echocardiography and right/left cardiac catheterization, classification is determined and an appropriate operative strategy initiated. Delay in surgical treatment is hazardous and will reduce early survival.

The surgical approach to most patients is based on the degree of RV hypoplasia and TV measurements (Table 70-1). Initial surgical management of most neonates with PA/IVS involves the establishment of a reliable and adequate source of pulmonary blood flow while optimizing the potential for growth and development of the RV and TV in order to achieve a biventricular repair later in life.

***Neonates with Mild Right Ventricular Hypoplasia.*** Neonates with PA/IVS and mild RV hypoplasia with a TV *Z*-score of 0 to −2 are best treated with a pulmonary valvotomy, insertion of an aorta-to-PA shunt, and ligation of the ductus arteriosus. Occasionally, there are patients in whom a pulmonary valvotomy alone will restore adequate pulmonary blood flow. Experience has shown that initial valvotomy alone often fails to produce effective palliation despite favorable anatomy. In most instances, it is preferable to perform a small shunt to ensure adequate pulmonary blood flow and promote subsequent growth of the branch PAs.

***Neonates with Moderate Right Ventricular Hypoplasia.*** Neonates with PA/IVS and moderate RV hypoplasia with a TV *Z*-score of −2 to −4 are best treated with a pulmonary valvotomy, patch augmentation of the pulmonary outflow tract, insertion of an aorta-to-PA shunt, and ligation of the ductus arteriosus. Pulmonary valvotomy and augmentation of the pulmonary outflow tract relieves RV hypertension, reduces tricuspid regurgitation, and potentiates the growth of both the tricuspid annulus and the RV cavity. In many patients with moderate RV hypoplasia, this may allow for a subsequent biventricular repair as the definitive procedure. A transannular pericardial patch (native or bovine) or Gore-Tex patch may be used to augment the RVOT.

***Neonates with Severe Right Ventricular Hypoplasia.*** Neonates with PA/IVS and severe RV hypoplasia with a TV *Z*-score less than −4 are more difficult to manage surgically. Balloon atrial septostomy is recommended at the time of cardiac catheterization, and stenting of the ductus arteriosus may be considered. Pulmonary valvotomy is usually not effective in relieving RV hypertension and augmenting pulmonary blood flow. If stenting of the ductus is not an option, these neonates are best treated with an aorta-to-PA shunt or a subclavian artery-to-PA (modified Blalock–Taussig) shunt. If there are no RV sinusoids or there are tortuous, narrow sinusoids without broad coronary artery fistulas, RV decompression by tricuspid valvotomy may be considered. This can be performed using a closed technique or with an open technique using cardiopulmonary bypass. In

most cases, decompression of the RV results in regression of the narrow, tortuous type of sinusoid and does not result in myocardial ischemia (if the native proximal coronary circulation is intact). If broad fistulas from the coronary arteries to the RV can be identified on the epicardial surface of the heart they can be directly ligated at the time of the shunt procedure.

## SPECIFIC OPERATIVE PROCEDURES FOR NEONATES

Below are described some specific surgical techniques utilized in patients with PA/IVS. Details on systemic-to-pulmonary shunts are presented in Chapter 68.

***Insertion of a Transannular Right Ventricular Outflow Tract Patch via Sternotomy.*** A transannular patch can be placed with relative ease on cardiopulmonary bypass, with aortic and RA cannulation and ligation of the ductus arteriosus. Advantages of performing a transannular patch with the use of cardiopulmonary bypass include better visualization of the annular area, more accurate placement of the edges of the patch, and little blood loss during opening of the RVOT with the RV decompressed.

In some cases with moderate RV hypoplasia, the infundibulum is long and narrow but reaches the pulmonary valve membrane. In these cases, a pericardial transannular patch may be inserted "off pump" without cardiopulmonary bypass (Fig. 70-2A–C). A median sternotomy incision is used. A pediatric cross clamp is placed immediately beneath the bifurcation of the PA. The ductus is kept open to provide pulmonary blood flow. A vertical incision is made in the main PA down to the RV junction. A partial-thickness incision is made over the RV for a distance to bring the incision over the RV cavity. Part of the muscle is resected to a depth of 2 to 3 mm to thin out the RV. A pericardial patch is then sutured to the pulmonary arteriotomy with running polypropylene down to the RV junction. The suture line is continued to the edges of the RV incision leaving the sutures loose inferiorly. A scalpel is then used to incise the valve membrane and to cut into the RV cavity under the pericardial patch. The sutures are pulled up to control bleeding, and the cross-clamp is removed. If the RV pressure is not adequately reduced, a rhizotomy knife is introduced through a purse-string suture in the pericardial patch, and the RV muscle is further incised until an adequate outflow tract has been created to reduce the RV pressure to an acceptable level. Advantages of this technique are the avoidance of cardiopulmonary bypass and also of systemic anticoagulation, although hemodynamic instability can limit the applicability of this technique to only very selected patients.

***Off-Pump Pulmonary Valvotomy via Left Thoracotomy.*** A pulmonary valvotomy may also be performed using a closed technique through a left thoracotomy. The approach is through the fourth intercostal space, with the lung retracted to expose the hilar region. The overlying pericardium is incised and the left PA identified. The main PA and PDA are then identified and the main PA is dissected from the surrounding tissue. Care is taken to avoid dissection of the PDA to maintain its patency during the procedure. The main PA is cross-clamped immediately below the bifurcation, allowing pulmonary perfusion to continue via the ductus arteriosus. The artery is then incised longitudinally and retracted to expose the valve. The fused commissures are identified and incised sharply with a No. 11 scalpel. A thin-bladed vascular C clamp is applied to the incision in the PA, and the cross clamp is removed. A Gore-Tex shunt can then be sutured to the main PA and to the subclavian artery using techniques similar to those used for a modified Blalock–Taussig shunt. The ductus arteriosus is ligated prior to releasing flow into the shunt. Pressure measurements can be obtained to assess the adequacy of the valvotomy and the potential need for further intervention to relieve the RV pressure.

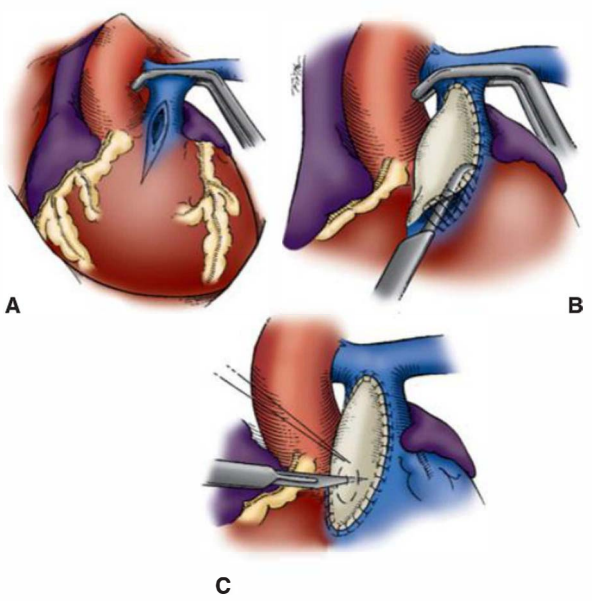



**FIGURE 70-2** Off-pump transannular pulmonary outflow tract pericardial patch. **A.** A cross clamp is placed on the main pulmonary artery as shown. The main pulmonary artery is incised and extended with a partial-thickness incision of the myocardium. **B.** The pericardial patch suture is left loose along the inferior edge until the annulus is divided and the right ventricular myocardium is completely incised into the outflow tract. **C.** Additional opening of the right ventricular outflow tract can be achieved with a No. 11 scalpel through a purse-string suture in the patch.

***Tricuspid Valvotomy.*** Tricuspid valvotomy is considered in patients with severe RV hypoplasia where the possibility of a subsequent biventricular repair is minimal. As mentioned above, preoperative catheterization must determine the absence of sinusoids or RVDCC prior to decompression of the RV. A tricuspid valvotomy can be performed through a median sternotomy using cardiopulmonary bypass and

cardoplegic myocardial arrest. Under direct visualization, the TV can be incised sharply at the commissural sites to allow decompression of the RV with resultant tricuspid valve regurgitation. An enlargement of the ASD can be performed if necessary to improve decompression of the right heart.

A closed technique of TV valvotomy has been described and may be indicated in cases where cardiopulmonary bypass should be avoided.[25] In many patients, decompression of the RV results in regression of the narrow, tortuous type of sinusoid and does not result in myocardial ischemia if the native circulation is intact.

## SURGICAL MANAGEMENT OF OLDER CHILDREN

Infants with PA/IVS are followed closely after their initial palliative procedures. With improving results, an increasing number of patients are presenting for later interventions. A cardiac catheterization is performed at 3 to 6 months of age, depending on the infant's initial morphology and subsequent echocardiographic findings. In patients with severe RV hypoplasia, repeat catheterization at 2 to 3 months is recommended as there may be a high mortality in this group while awaiting repair. The selection of operative procedures is based primarily on RV morphology and on assessment of the TV and RV growth since the previous intervention. In many patients, continued growth of the TV and RV will be comparable and relatively similar, making decisions about definitive repair easier. Disparity of growth between the TV and the RV cavity can lead to difficult decisions about subsequent procedures. Whereas in neonates the size of the TV and the RV usually correlate quite well, in older children there can be a significant discrepancy between these two measurements. Definitive procedures will be determined based on the anatomic findings at catheterization. These patients are again divided into those with mild, moderate, or severe RV hypoplasia (Table 70-2).

The use of an adjustable snare to close the ASD permits control of right-to-left shunting at the atrial level in children where RV volume and compliance may limit forward RV outflow to the pulmonary arteries. The ability to adjust the size of the ASD allows for postoperative control of right-to-left shunting and for the adjustment of forward flow through the RV.[31,32] This can be very helpful in optimizing RV output and avoiding excessive cyanosis.

***Biventricular Repair for Patients with Mild Right Ventricular Hypoplasia.*** In patients with mild RV hypoplasia, later surgical intervention often includes closure of the ASD with an adjustable snare, enlargement of the RV cavity and outflow tract by myocardial resection, and patch augmentation of the RVOT. In order to achieve a competent pulmonary valve, either a pericardial monocusp valve or a bioprosthetic tissue valve is inserted in the RVOT. Use of a homograph pulmonary valved conduit or a Contegra bovine jugular vein valved conduit may also be considered. A successful biventricular repair is achieved in the majority of these patients. Some patients with mild hypoplasia treated by valvotomy may not require subsequent surgery unless the obstruction to the outflow tract has recurred.

**TABLE 70-2: Surgical Management for Definitive Repair of Patients with Pulmonary Atresia with Intact Ventricular Septum**

| Classification of RV Hypoplasia | Treatment Options |
|---|---|
| Mild | Closure of ASD (adjustable snare), enlargement of RV and RVOT, and transannular patch with monocusp valve. Ligation of previous shunt. |
| | Closure of ASD (adjustable snare), enlargement of RV and RVOT, and valved pulmonary homograft. Ligation of previous shunt. |
| Moderate | Closure of ASD (adjustable snare), bidirectional Glenn shunt, enlargement of RV and RVOT, and transannular patch with oversized bioprosthetic valve. Ligation of previous shunt. |
| | Closure of ASD (adjustable snare), bidirectional Glenn shunt, enlargement of RV and RVOT, and valved pulmonary homograft. Ligation of previous shunt. |
| Severe | Staged bidirectional Glenn shunt for later Fontan procedure. |
| | Adjustable ASD. Partial ligation of previous shunt. |
| | Fontan with adjustable ASD. Ligation of previous shunt. |

ASD, atrial septal defect; RV, right ventricle; RVOT, right venticular outflow tract.

***Biventricular and Partial Biventricular Repair for Patients with Moderate Right Ventricular Hypoplasia.*** In the patient with moderate RV and TV hypoplasia, definitive repair is dictated by the previous growth and development of the RV and the TV. If the TV diameter is one-half to two-thirds normal size, repair will then consist of partial closure of the ASD with an adjustable snare, enlargement of the RV cavity by myocardial resection, and insertion of a valved conduit between the RV and the PA. If the TV diameter is one-third to one-half of normal, then repair will consist of partial closure of the ASD with an adjustable snare, enlargement of the RV cavity, creation of a bidirectional Glenn cavopulmonary shunt, and insertion of a valved conduit between the RV and PA. The bidirectional Glenn cavopulmonary shunt reduces the volume load on the small RV and provides an obligatory source of pulmonary blood flow. This allows the channeling of approximately one-third of the systemic venous return from the superior vena cava (SVC) directly to the pulmonary arteries while the inferior vena cava (IVC) (two-thirds of the systemic venous return in small children) continues to pass through the TV and RV. This has been termed the "one-and-one-half ventricle" or "partial biventricular" repair. The ASD

is adjustable to create a gradient between RA and left atrium to encourage forward flow through the RV. This will in turn enhance its development (as well as that of the TV) and increase the likelihood of a subsequent two-ventricle repair. Based on the growth of the RV and the TV, either a two-ventricle repair can be achieved (with takedown of the Glenn shunt) or a single ventricle repair with Fontan completion.

***Staged Fontan Procedure for Patients with Severe Right Ventricular Hypoplasia.*** In patients with PA/IVS and severe RV and TV hypoplasia, a biventricular repair is usually not possible. Most of these patients will have undergone placement of a systemic-to-PA shunt in the neonatal period with or without tricuspid valvotomy, depending on the presence or absence of RVDCC. The bidirectional Glenn cavopulmonary anastomosis is performed in the first 3 to 6 months of life with a plan for a total cavopulmonary connection within the first 3 to 4 years of life. Fenestration of the Fontan circuit may be used as an ASD with an adjustable snare when a lateral tunnel technique is utilized (see Chapter 77). The Fontan may be performed either as a lateral tunnel or as an extracardiac conduit. Both types of Fontan procedures can be constructed with an effective adjustable fenestration to the atrial chamber.

***Surgical Management of Children with PA/IVS with Ebstein's Malformation.*** Ebstein's malformation of the TV is present in 10 percent of patients with PA/IVS. This group of neonates should be considered separately. Most of these patients will have severe TV insufficiency and a normal-sized or enlarged RV. There is also massive dilatation of the RA. The LV function is often compromised in these infants because of the dilated dysfunctional RV and septal shift into the LV cavity. Although an aorta-to-PA shunt may establish adequate pulmonary blood flow, LV output often remains compromised by the dilated RV. Surgical intervention in these patients is associated with greater than 50 percent mortality.[33] Orthotopic heart transplantation should be considered as an initial therapeutic option in these patients.

***Surgical Management of Children with Right Ventricle-Dependent Coronary Circulation.*** A RVDCC is one in which there are sinusoidal connections between the cavity of the RV and the coronary circulation, either with obstruction in the native coronary circulation or with broad sinusoidal connections that would result in runoff from the coronary circulation into the low-pressure RV. Tortuous sinusoidal connections without coronary stenoses do not usually denote a RVDCC. Decompression of the RV at the time of the bidirectional Glenn anastomosis will usually result in closure of these sinusoids as opposed to the broad-based fistulous connections. In some cases, the large fistulous connections can be identified on the surface of the heart and be suture ligated at the time of the bidirectional Glenn shunt, allowing RV decompression at that time.

In infants with RVDCC, systemic RV pressure must be maintained to ensure adequate coronary perfusion to the myocardium.[34] Even in older children, decompression of the RV by augmentation of the outflow tract or tricuspid valvotomy may lead to severe myocardial ischemia and acute cardiac failure. If a RVDCC is identified, a single-ventricle surgical strategy is pursued and a bidirectional Glenn anastomosis performed at 3 to 6 months of age without RV decompression. Any additional source of pulmonary blood flow, such as a previously placed shunt, may be reduced or ligated at the time of the Glenn procedure. At 2 to 4 years of age, the Fontan completion is carried out. In order to bring oxygenated blood to the TV, the atrial septum is excised and the coronary sinus unroofed at the time of Fontan completion.

If there are signs of myocardial ischemia either preoperatively or intraoperatively, the RVDCC may be improved by creating an aortic-to-RV shunt.[35] This shunt theoretically changes the RV systolic pressure to equal the systemic pressure, elevating the diastolic pressure and maintaining coronary perfusion. Flow through such a shunt appears to be bidirectional and biphasic. Experience to date has been limited with this technique, and long-term follow-up is not yet available. If myocardial ischemia results from decompression of an undiagnosed RVDCC, coronary artery bypass grafting using the internal mammary artery may be attempted. Unfortunately, the use of coronary artery bypass grafting in these patients is limited by technical difficulties, conduit options, and limited long-term graft patency.

Finally, in patients with RVDCC and severe RV dysfunction, early shunt placement may be followed by consideration of orthotopic heart transplantation.

## SPECIFIC OPERATIVE PROCEDURES IN OLDER CHILDREN

***Enlargement of the Right Ventricular Cavity and Right Ventricular Outflow Tract.*** The RV cavity is enlarged by using cardiopulmonary bypass with bicaval cannulation and cardioplegic arrest to sharply resect trabecular muscle. The RA is opened longitudinally and the TV inspected; the annulus is measured and compared to normal values and its competence tested with cold saline. An incision is made longitudinally from the main PA through the annulus and across the infundibulum to the main RV cavity. The cavity is enlarged by resection of trabecular muscle under direct vision. Care is taken to work between the papillary muscles, which should be avoided. A glutaraldehyde-treated pericardial outflow patch is then placed on the RV incision. In infants, we generally prefer a pericardial patch with a monocusp valve. In older children, we have used a porcine valve within the RVOT or an RV to PA conduit.

***Adjustable Atrial Septal Defect.*** If the ASD is large, it is closed with a Gore-Tex vascular patch. If the defect is small with firm edges, it may be closed with the purse-string suture of the "adjustable ASD." The adjustable ASD is created by placing a No. 1 polypropylene suture as a purse string around the tissue edges of the existing septal defect, with a pericar-

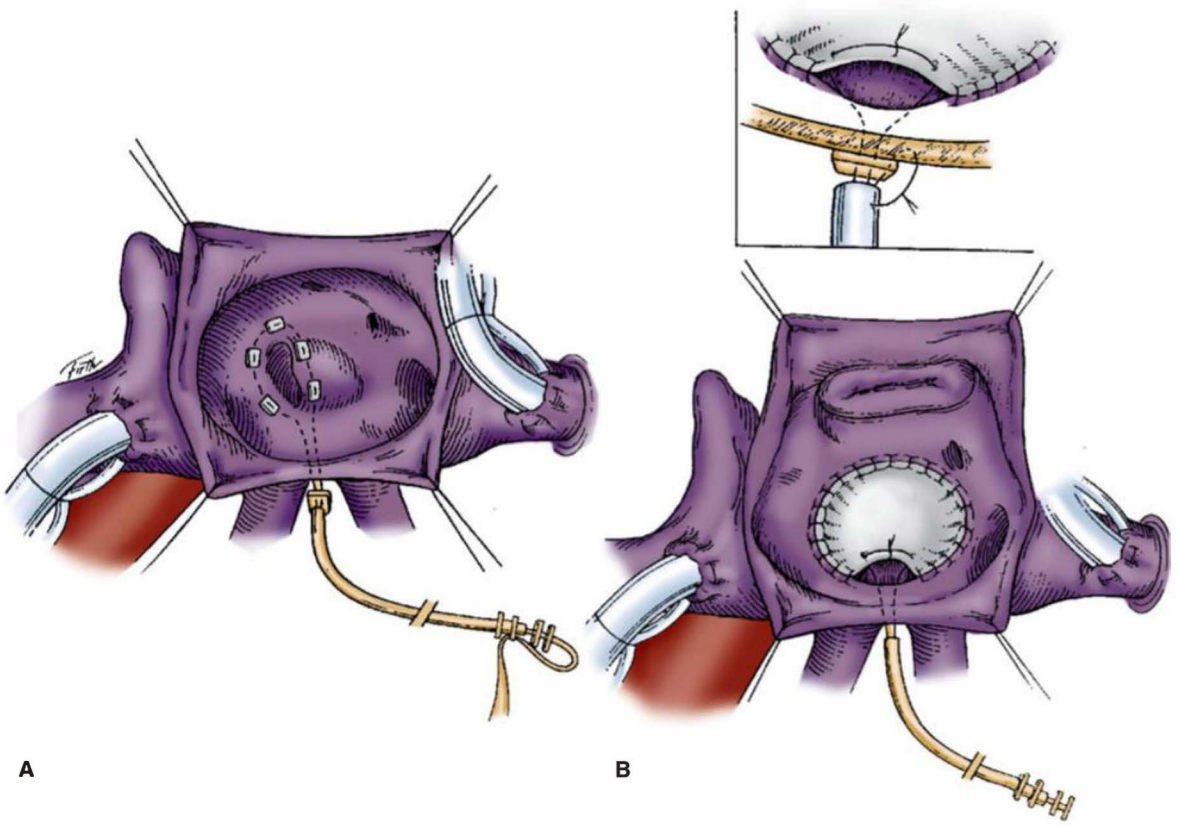



**FIGURE 70-3** Adjustable atrial septal defect with and without patch closure of the native atrial septal defect. **A.** A No. 1 polypropylene purse-string suture is secured around the border of the atrial septal defect using pericardial or felt pledgets. The snare is constructed using 8F polyethylene tubing placed over the No. 1 polypropylene suture and measured to reach the linea alba. **B.** If a large secundum atrial septal defect is present, it is closed with a Gore-Tex or pericardial patch, and a defect is left in the lateral wall. A No. 1 polypropylene suture is brought in through the interatrial groove and placed as a horizontal mattress stitch through the edge of the patch. The No. 1 polypropylene suture is then anchored to the edge of the patch with a 5-0 polypropylene suture.

dial pledget used as a reinforcement. Both ends of the suture are then brought out through the interatrial groove. An 8F polyethylene tube is cut to length to reach the linea alba and passed over the ends of the polypropylene suture to construct the snare. The tubing is sutured to the atrial wall with a single chromic suture (Fig. 70-3A). The snare is adjusted by tightening or loosening the polypropylene suture at the end of the tubing and securing the length with medium clips. The end of the snare is left under the subxiphoid linea alba, where it can be retrieved under local anesthesia postoperatively for subsequent adjustment. The same technique can be used to create an adjustable defect in a Gore-Tex (expanded polytetrafluoroethylene or ePTFE) patch. The defect in the suture line is left on the right side where it is surrounded by a polypropylene suture as described above (Fig. 70-3B). The ASD is left open until the patient is weaned from bypass. The ASD is then slowly closed, using the snare while monitoring the RA pressure and arterial oxygen saturations. A target RA pressure of about 12 to 14 mm Hg with an oxygen saturation of 88 percent or above on 100 percent inspired oxygen is considered optimal.

***Bioprosthetic Valve Insertion with Transannular Patch.*** A transannular incision is made vertically across the pulmonary outflow tract and extended onto the left PA and down into the RV. Any residual membrane in the region of the annulus is resected. The distance between the RVOT and the PA bifurcation is assessed. If it is short, use of a homograft may not be possible, as the proximity of the proximal and distal suture lines will result in bulging of the homograft. For this situation, a larger porcine valve can be placed under a pericardial (autologous or bovine) patch within the RVOT. The porcine valve may be implanted at the level of the native valve annulus (Fig. 70-4A) or in the subvalvular region below the level of the true pulmonary annulus (Fig. 70-4B) to accommodate a larger valve and reduce the amount of

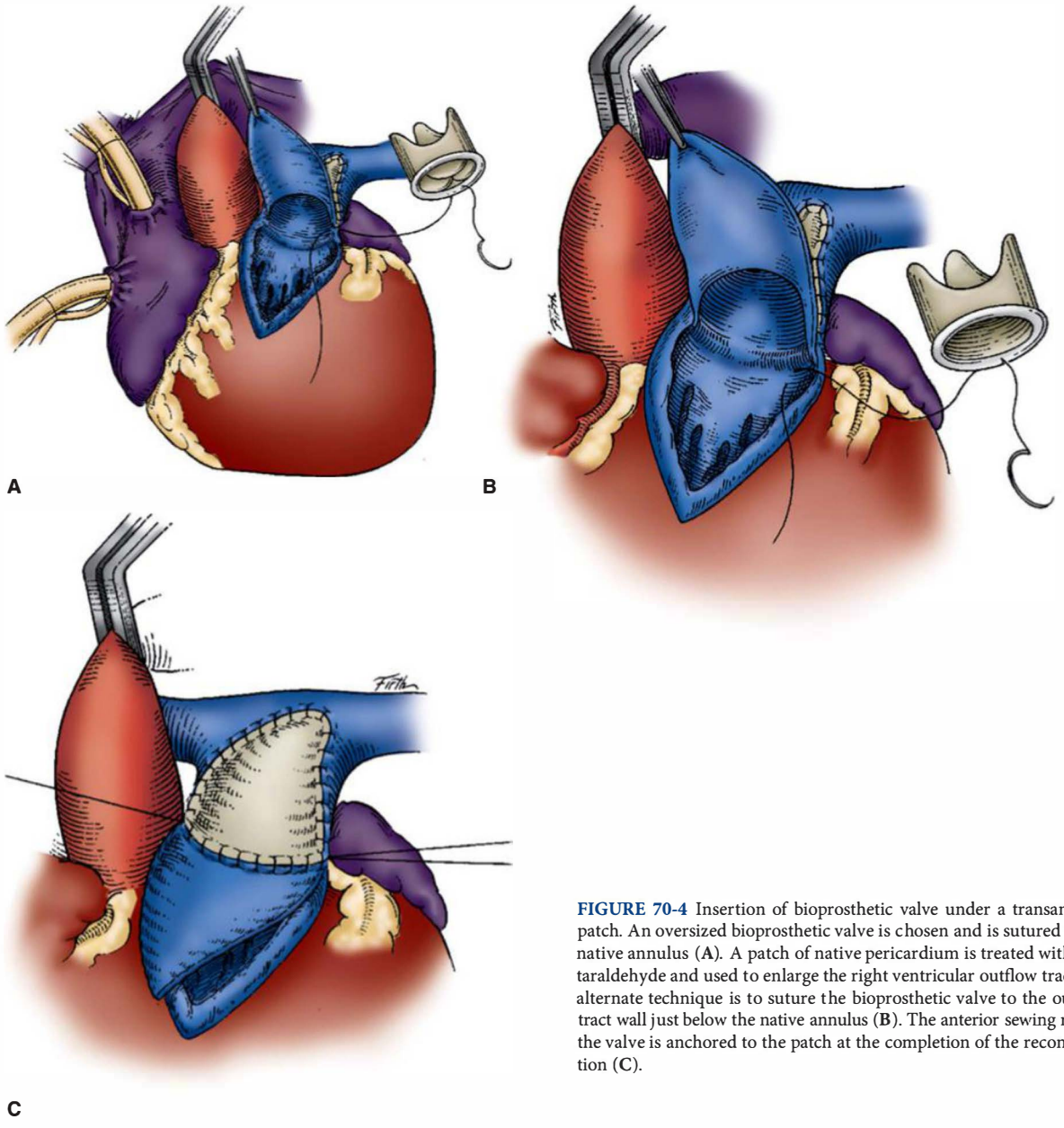



**FIGURE 70-4** Insertion of bioprosthetic valve under a transannular patch. An oversized bioprosthetic valve is chosen and is sutured to the native annulus (**A**). A patch of native pericardium is treated with glutaraldehyde and used to enlarge the right ventricular outflow tract. An alternate technique is to suture the bioprosthetic valve to the outflow tract wall just below the native annulus (**B**). The anterior sewing ring of the valve is anchored to the patch at the completion of the reconstruction (**C**).

compression that may result from closure of the sternum. A running polypropylene suture is used to insert the valve, which is also sutured to the patch anteriorly (Fig. 70-4C).

***Homograft Valve Insertion.*** If the distance between the RVOT and the PA bifurcation is adequate, an appropriate aortic or pulmonary homograft is chosen. A running polypropylene suture is used distally just below the PA bifurcation. Proximally, the homograft is sutured to the RVOT just below the pulmonary valve with a running suture. The proximal anastomosis of the homograft and the RVOT are augmented with a pericardial or synthetic (ePTFE or Dacron) patch.

***Transannular Patch with Pericardial Monocusp Valve.*** This technique is used for neonates and infants but can also be used for small children. It should be used for patients with mild or moderate RV hypoplasia and with acceptable PA size as the valve will remain competent for a shorter period of time than a complete tissue valve. It has the advantage,

however, of rarely causing obstruction even when the valve has become incompetent.

***Bidirectional Glenn Cavopulmonary Shunt.*** A median sternotomy incision is used for a Glenn cavopulmonary anastomosis. The right PA and SVC are dissected free from surrounding tissues and the azygos vein is divided between ligatures. Excessive dissection in this region may disrupt lymphatic tissue and result in postoperative chylothorax. The PA pressure is measured on both sides. A left SVC may be identified anterior to the left PA. The SVC is clamped just above the RA and the proximal pressure is monitored. If the pressure does not rise above a mean of 30 mm Hg, a left SVC should be suspected (as it would be in case of absence of the left innominate vein). If both right and left SVCs are present, cardiopulmonary bypass or a temporary shunt may not be necessary. If the proximal pressure in the clamped SVC is 30 mm Hg or greater, a temporary shunt should be used. A vertical purse-string suture is placed on the SVC at its junction with the innominate vein. A second purse-string suture is placed in the RA appendage. The patient is heparinized and a temporary bypass shunt is created using two venous cannulae and a Y connector with a *chapeau* attachment. The SVC is cannulated with the bevel of the cannula placed toward the right internal jugular vein. The second cannula is placed in the RA appendage. The circuit is connected after air is completely evacuated from the cannulae and the clamps are removed, with visualization of flow. The SVC is then clamped at its junctions with the RA and the innominate vein. The anterior aspect of the SVC and the superior margin of the right PA are marked to ensure proper alignment of the cavopulmonary anastomosis. The SVC is divided at the atrial junction and the open end of the SVC is enlarged by an incision in the posterior wall of the vessel. The anastomosis is performed with a running 6-0 or 7-0 polypropylene suture (Fig. 70-5).

Any previously placed systemic-to-PA shunt is now reduced in size or eliminated to give an estimated $Q_p$:$Q_s$ of 1.3:1 or less. The SVC and PA pressures are measured, as well as the arterial oxygen saturations on 100 percent oxygen.

***Lateral Tunnel Fontan with Adjustable Atrial Septal Defect.*** A Fontan procedure is usually performed as a second- or third-stage operation. A median sternotomy is performed and bicaval venous cannulation between the SVC and IVC is carried out. Systemic hypothermia to 32°C is used in addition to cold blood cardioplegic arrest.

A right atriotomy is performed just anterior to the linea terminalis and the edges are retracted with stay sutures. The coronary sinus is identified and cannulated with a retrograde cardioplegia catheter. Cold blood cardioplegia is delivered intermittently both antegrade and retrograde.

The atrial septum is excised. The SVC orifice is identified from within the RA. It is important that this orifice be widely open and not restrictive. The right PA is incised adjacent to the opening in the SVC stump. The posterior wall of

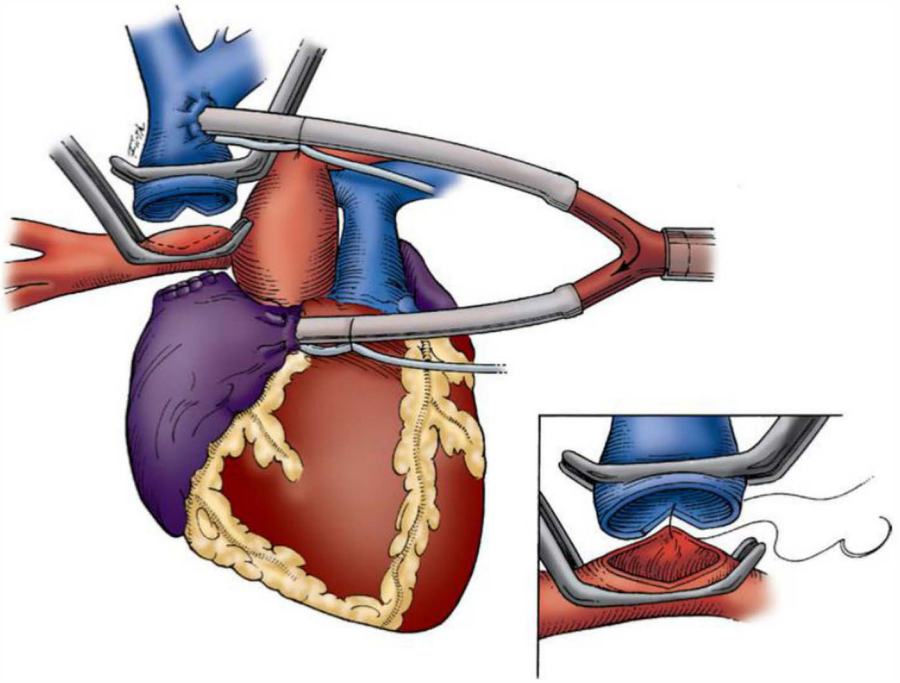


**FIGURE 70-5** Bidirectional Glenn shunt. The Glenn shunt operation is performed using a superior vena cava–to–pulmonary artery shunt. The cannulae are placed in the superior vena cava and the right atrium, allowing continuous flow of venous return to the right atrium during the reconstruction. To avoid stenosis, the anastomosis is tailored as shown in the insert.

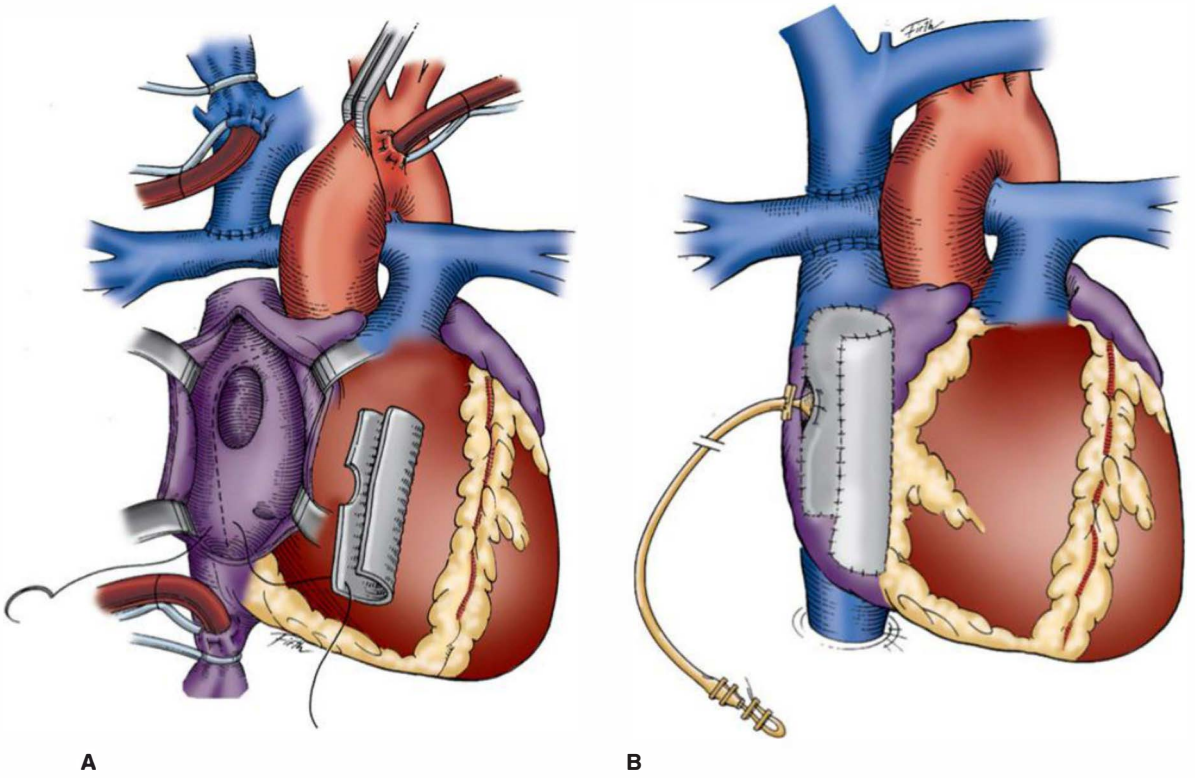



**FIGURE 70-6** Lateral tunnel Fontan with an adjustable atrial septal defect. A tunnel of uniform caliber is constructed by suturing a Gore-Tex vascular patch to the orifice of the inferior vena cava and the superior vena cava and to the lateral atrial wall (**A**). A defect is left in the tunnel and an adjustable atrial septal defect is achieved by passing a No. 1 polypropylene suture through the lateral portion of the interatrial septum and through the edge of the Gore-Tex tunnel. The No. 1 polypropylene suture is then secured to the edge of the Gore-Tex with a 5-0 polypropylene suture. The suture is brought back out the interatrial septum and through a pericardial pledget. The snare is constructed with a No. 8F polyethylene tubing and anchored to the heart through a pledget as shown (**B**). The completed lateral tunnel Fontan reconstruction is shown with the adjustable atrial septal defect left open.

the anastomosis is created by suturing the adjacent PA and RA together with polypropylene suture. Anteriorly, the connection is bridged with a pericardial patch to assure patency without obstruction.

After the RA-to-PA anastomosis has been completed, the lateral tunnel is constructed. A rectangular Gore-Tex patch is cut from 0.8-mm-thick Gore-Tex vascular patch material. The length is carefully measured from the orifice of the IVC to that of the SVC. The width is left about two-thirds of the length to be trimmed after completion of the posterior suture line. A running polypropylene suture is used for the posterior suture line, which is begun at the IVC orifice (Fig. 70-6A). The suture line is carried superiorly to the site of the orifice of the adjustable ASD where it ends. This site is chosen because it comprises a natural recess close to the right superior pulmonary vein at the superior and lateral end of the fossa ovalis. A second polypropylene suture line is begun at the superior end of the ASD defect and carried superiorly around the SVC orifice. The ASD is sized according to the patient's age and made large in diameter so that it may be reduced in size if necessary after the patient comes off bypass. As a rule of thumb, the defect's size is 4 mm for 2-year olds, 6 mm for 4-year olds, and 8 mm for children 6 years old and older. The patch is trimmed appropriately as the suture line advances. Before the anterior suture line is completed, the snare control is placed for the adjustable ASD. A No. 1 polypropylene suture is brought through a pericardial pledget, through the interatrial septum at the lower border of the ASD, and through the edge of the Gore-Tex patch. It is then brought back through the upper edge of the Gore-Tex patch and out through the interatrial septum and through the pericardial pledget. An 8F polyethylene tube is cut to the appropriate length to reach the linea alba and the polypropylene sutures are brought through this snare. The No. 1 polypropylene is sutured to the edge of the Gore-Tex patch with a 5-0 polypropylene suture, the polyethylene tubing is sutured to the lateral wall with 2-0 chromic catgut, and the polypropylene is fixed to the heavy polypropylene with a medium-size clip. These three points of fixation prevent inadvertent closure of the ASD by tugging on the polypropylene. The patch is now trimmed to create a wide-open connection and to reach just anterior to

the linea terminalis. The anterior part of the suture line is completed using full thickness sutures to avoid a suture-line leak. The RA incision is then closed with a polypropylene suture (Fig. 70-6B).

Transthoracic lines are generally placed in the left and right atria. If an internal jugular line is not inserted, the RA line can be inserted to measure the pressure in the pulmonary system via the Fontan tunnel or the Glenn anastomosis. The patient is weaned from cardiopulmonary bypass and the ASD snare is adjusted to achieve arterial saturations of 80 to 85 percent with an $FIO_2$ of 50 percent while attempting to maintain pressure in the Fontan circuit at or below 16 mm Hg.

***Extracardiac Fontan with Adjustable Atrial Septal Defect.*** The extracardiac Fontan is performed through a median sternotomy using cardiopulmonary bypass and bicaval cannulation. The procedure can be completed in most patients without the need for cardioplegic arrest of the heart. A clamp is placed on the IVC near its junction to the RA. The IVC is then divided between the snared venous cannula and the clamp. The atrium is repaired and the clamp is removed.

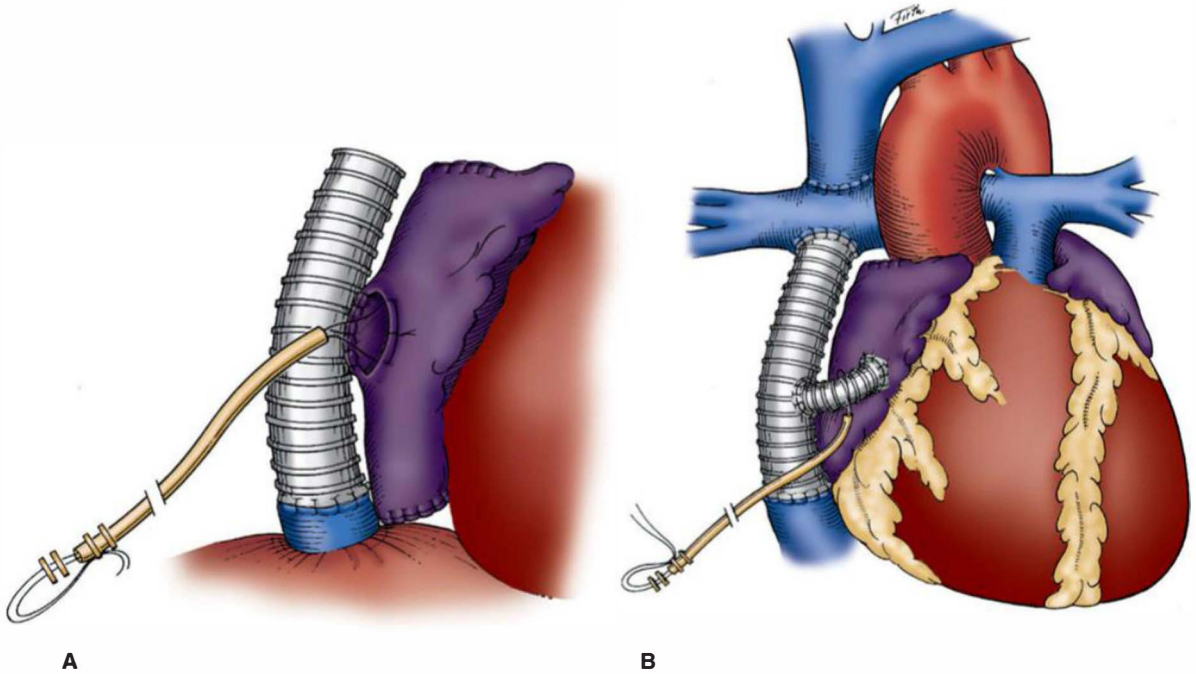
The open end of the IVC is anastomosed end-to-end to a Gore-Tex conduit (16–20 mm in diameter) using a running Gore-Tex suture. The proximal anastomosis is performed end-to-side between the Gore-Tex conduit and the inferior aspect of the right PA. The clamps are released and flow is established between the IVC and the pulmonary arteries.

To create the adjustable fenestration, a partially occluding vascular C clamp is placed on the Gore-Tex graft. A direct anastomosis is performed between the extracardiac conduit and the RA. A snare is inserted to control the opening and closing of this "ASD" (Fig. 70-7A). An alternate method uses a conduit for the defect. With this technique an 8 mm Gore-Tex graft is anastomosed end-to-side to the middle of the larger conduit. A similar technique is used to create an opening in the RA and the other end of the 8 mm graft is anastomosed to this site. A snare is inserted around the smaller conduit (Fig. 70-7B). A distinct drawback to the extracardiac Fontan is the need for anticoagulation with warfarin postoperatively for up to a year, with subsequent conversion to aspirin therapy.

## COURSE AND PROGNOSIS

### Postoperative Care in Neonates

Neonates may be critically ill in the early postoperative period following operative intervention for PA/IVS. The presence of low cardiac output may require substantial inotropic



A B

**FIGURE 70-7** Extracardiac Fontan with an adjustable fenestration. The extracardiac conduit is implanted and a direct anastomosis is made between the conduit and the atrial wall. The defect is controlled with an adjustable snare (**A**). The extracardiac conduit is implanted and a communication is established between the conduit and the atrium using an 8 mm Gore-Tex graft. The graft diameter is then controlled by an adjustable snare (**B**).

support. In the presence of a systemic-to-PA shunt, balanced pulmonary and systemic blood flow must be achieved. The management of pulmonary and systemic vascular resistance is critical to maintaining adequate oxygenation and cardiac output. Episodes of pulmonary hypertension must be managed quickly and may require the use of inhaled nitric oxide. An excessively large shunt may lead to pulmonary overcirculation and require adjustment or replacement of the shunt. Postoperative ischemia can develop due to unrecognized RVDCC and may be associated with electrocardiographic changes, ventricular dysrhythmias, and segmental wall dyskinesia on echocardiography. In patients with persistent hypoxemia despite adequate medical management, residual RVOT obstruction or severe tricuspid hypoplasia should be excluded.

### Postoperative Care in Older Children

Early management after the Fontan procedure should focus on optimizing cardiac output and reducing systemic venous pressure. Inotropes are routinely used, starting with dopamine and dobutamine. If additional inotropic support is needed, milrinone may be added. If systemic vascular resistance is low and additional inotropic support is required, the use of epinephrine may be indicated. The adjustable ASD is useful because it allows as much as one-third of the systemic venous return to traverse the ASD, thus lowering the systemic venous pressure while increasing LV preload and the cardiac output. With a $Q_P$:$Q_S$ ratio of 1.5:1, the arterial oxygen saturation should be approximately 85 percent. A systemic venous pressure of 12 to 15 mm Hg is optimal. It should be noted that the presence of a patent right-to-left shunt increases the risk of paradoxical emboli from thrombus, which may develop in the RA or the hepatic veins. Therefore, complete closure of the adjustable ASD should be performed when it is hemodynamically tolerated.

If pulmonary vascular resistance is elevated postoperatively following a Glenn or Fontan procedure, it is reduced in our practice with an infusion of nitroglycerin and $PGE_1$. These medications are more effective in lowering pulmonary vascular resistance if delivered directly into a catheter in the Glenn or Fontan circuit. If these medications are not sufficient, nitric oxide is administered through the ventilator. Unlike intravenous medications, nitric oxide does not result in the lowering of systemic vascular resistance.

Extubation within the first 24 h is generally attempted after both Glenn and Fontan procedures. The development of pleural and pericardial effusions is anticipated, and mediastinal and pleural chest tubes are left in place for several days postoperatively until drainage is minimal.

If a jugular vein line has been inserted, it is used for measuring the PA pressure and for the infusion of pulmonary vasodilators if necessary. The line is removed within 12 hours to avoid venous thrombosis.

## OUTCOMES

Historically, the surgical treatment of PA/IVS was associated with very high morbidity and mortality.[5,36] Previous extensive reviews of the clinical and pathologic aspects of this malformation have allowed for a greater understanding of the disease and for the development of surgical therapy.[37] With increasing surgical experience, a more standardized approach has evolved and outcomes from many institutions have steadily improved.[38–44] The role of catheter-based interventions in these patients, including balloon valvotomy and stenting of the RVOT and the ductus arteriosus, is evolving and remains to be defined.[45]

In the CHSS multi-institutional study, 408 neonates with PA/IVS were studied from 33 institutions. Overall survival was 77 percent at 1 month, 70 percent at 6 months, 60 percent at 5 years, and 58 percent at 15 years. Prevalence of end states at 15 years were as follows: two-ventricle repair, 33 percent; Fontan palliation, 20 percent; one-and-a-half ventricle repair, 5 percent; heart transplant, 2 percent; death before reaching definitive repair, 38 percent; and alive without definitive repair, 2 percent. The authors concluded that 85 percent of neonates with PA/IVS are likely to reach a definitive surgical repair or palliation, with a two-ventricle repair achieved in an estimated 50 percent and a Fontan circulation achieved in 35 percent in the current era.[46]

### Future Considerations

Transcatheter therapy in patients with PA/IVS is becoming a more common approach to initial interventions in neonates. These techniques include radiofrequency valvotomy, PDA stenting, RVOT stenting, and device closure of ASD. As experience increases, these techniques are gaining wider acceptance as alternatives to or complements to surgery in treatment options.[47–49] Various hybrid approaches may emerge combining both surgical and catheter-based interventions. In some studies, catheter-based interventions in neonates have rarely avoided surgical interventions.[50,51]

In utero perforation and dilatation of the PV in midgestational fetuses with PA/IVS has been reported in a limited experience.[52] The overall effect of this type of fetal intervention on subsequent growth and development of the RV and its clinical impact on outcomes in patients with PA/IVS remains to be defined.

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## PULMONARY STENOSIS AND PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM BOARD REVIEW QUESTIONS (CHAPTER 70)

1. Which is correct regarding pulmonary stenosis?
   A. The valve is typically flat with central leaflet fusion.
   B. The RV is usually smaller than normal.
   C. The pulmonary annulus is either normal or smaller than expected.
   D. If the RV is enlarged, this portends a better prognosis.
   E. Intervention is indicated with a mean gradient above 30 mm Hg.

2. Which is true regarding treatment of pulmonary stenosis?
   A. Permissive systemic hypotension is useful to reduce ductal flow.
   B. Inotropic agents will increase flow across the RVOT.
   C. Open valvotomy should extend to the edge of the annulus.
   D. A partial valvectomy should be avoided.
   E. Dilators can rupture the infundibulum.

3. Which is correct regarding PA with IVS (PA–IVS)?
   A. Surgical approach is primarily based on the degree of RV hypertrophy.
   B. Untreated patients have a mortality approaching 85 percent at 6 months.
   C. RV-to-coronary artery fistulas are more common in patients with a severely enlarged RV and an incompetent tricuspid valve.
   D. Pulmonary blood flow is almost entirely dependent on an ASD.
   E. Ebstein's malformation is not seen in PA–IVS.

4. Which is correct regarding PA–IVS and RV hypoplasia?
   A. Neonates with mild RV hypoplasia are best treated with pulmonary valvotomy and patch augmentation of the RVOT.
   B. Neonates with moderate RV hypoplasia are best treated with pulmonary valvotomy and a systemic-pulmonary shunt.
   C. Pulmonary valvotomy is usually sufficient in relieving RV hypertension in patients with severe RV hypoplasia.
   D. Decompression of the RV does not result in regression of narrow sinusoids.
   E. Broad fistulas to the RV can be directly ligated on the surface of the heart.

5. Which is true regarding outcomes for PS and PA–IVS?
   A. Following surgical correction of PS, there is often a residual gradient.
   B. Ten percent of PS patients will require reintervention within 2 years for residual stenosis.
   C. Overall survival after surgery for PA–IVS is 90 percent at 5 years.
   D. Most patients with PA–IVS will die before reaching definitive repair.
   E. Fontan repair is the most common pathway in the current era.

## ANSWERS

1. **Answer: C.** The pulmonary annulus is either normal or smaller than expected. The valve is typically dome shaped with commissural fusion. The RV is usually of normal size; if enlarged, this is associated with a very poor prognosis. Intervention is indicated with a mean gradient exceeding 50 mm Hg.
2. **Answer: C.** Open valvotomy should extend to the edge of the annulus. Systemic hypotension should be avoided, as this will reduce ductal flow and worsen hypoxemia. Inotropic agents can worsen functional obstruction of the RVOT. Partial valvectomy may be necessary to remove thickened valve tissue or fibrous scar. Dilators are useful to size the annulus and dilate the annular tissue.
3. **Answer: B.** Untreated patients have a mortality approaching 85 percent at 6 months. The surgical approach is primarily based on the degree of RV and TV hypoplasia. RV to coronary artery fistulas are more common in patients with a severely hypoplastic RV and a competent tricuspid valve. Pulmonary blood flow is almost entirely dependent on a PDA. Ebstein's malformation is seen in about 10 percent of patients.
4. **Answer: E.** Broad fistulas to the RV can be directly ligated on the surface of the heart at the time of shunting. Neonates with mild RV hypoplasia are best treated with pulmonary valvotomy and a systemic–pulmonary shunt, whereas patients with moderate RV hypoplasia will require patch augmentation of the RVOT. Pulmonary valvotomy is usually not effective in relieving RV hypertension in patients with severe RV hypoplasia. Decompression of the RV generally results in regression of narrow sinusoids.
5. **Answer: A.** Following surgical correction of PS, there is often a residual gradient across the RVOT. About 25 percent of PS patients will require reintervention within 2 years for residual stenosis. Overall survival after surgery for PA–IVS is 60 percent at 5 years. About 40 percent of PA–IVS patients will die before reaching definitive repair. Two-ventricle repair is the most common pathway, with about 50 percent of patients achieving this result.

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# 71 Double Outlet Right Ventricle

*Jess Thompson*
*Joseph A. Dearani*

## KEY CONCEPTS

- Epidemiology
  - Relatively uncommon congenital anomaly seen in 0.09 in 1000 births
- Pathophysiology
  - Considerable variability in pathophysiology is seen with double outlet right ventricle (DORV) and is primarily dependent on the location of the ventricular septal defect (VSD), the relationship of the great arteries and the presence of great vessel stenosis
- Clinical features
  - Patients usually present by age 2 months (range 1 day–4 years). Presentation is variable and is dependent on the type of DORV and associated cardiac anomalies. Heart failure is seen in patients with unrestricted subaortic, doubly-committed or non-committed VSDs without right ventricular outflow tract obstruction (RVOTO). Cyanosis results from RVOTO leading to restriction of pulmonary blood flow or by preferential streaming of blood from the left ventricle (LV) to pulmonary artery (PA) as seen in the Taussig–Bing anomaly.
- Diagnosis
  - Echocardiography defines the relationship of the great arteries to the right ventricle (RV) and to each other, and delineates the size and position of the VSD. MRI may provide complementary information about intracardiac anatomy, size and status of the aortic arch and PAs, and 3-dimensional relationship of chambers and great arteries. Catheterization can be performed to determine hemodynamics, exclude pulmonary vascular disease and assess coronary anatomy.
- Treatment
  - Definitive management includes operation, preferably complete repair during infancy. The surgical repair is tailored to address the variable anatomical abnormalities. In patients with a subaortic or doubly-committed VSD without RVOTO, the repair is performed with an intraventricular tunnel from the VSD to the aorta. If RVOTO exists, right ventricular outflow tract (RVOT) augmentation or conduit placement is performed. The Taussig–Bing anomaly is treated with the arterial switch operation and tunneling of the VSD to the PA. Patients with a remote VSD, other complex valve abnormalities or unbalanced ventricles may require staged palliative single ventricle procedures.
- Outcomes/prognosis
  - Outcomes are determined by the anatomy and the repair performed. Late results may range from those of tetralogy of Fallot to those of complex intraventricular tunnels, with potential use of conduit, who are at subsequent risk for subaortic obstruction, conduit failure, and need for reoperation(s). Patients undergoing the arterial switch operation have excellent late survival but may have a greater incidence of neoaortic valve regurgitation requiring subsequent reoperation. Complex biventricular intracardiac repairs are associated with a higher operative risk and the potential need for reoperations. Fontan procedures for complex anatomy are associated with less operative mortality and lower reoperation rates. Functional benefits of complex biventricular repairs compared to single-ventricle palliation have not been defined.

# INTRODUCTION/BACKGROUND

## Definition

Double outlet right ventricle (DORV) is best defined as an anomaly of cono-truncal development that results in both great arteries arising entirely or predominantly from the right ventricle (RV).[1] Consequently, DORV is not a specific congenital malformation; rather DORV is a descriptive term used to define the relationship of the great arteries to the RV. Most authors agree that the degree of aortic override of the RV has to be at least 50 percent and that the only outlet of blood from the left ventricle (LV) is the ventricular septal defect (VSD).[2]

## Historical Highlights

Although cases of DORV were documented in the mid-19th century,[3,4] the term "double outlet ventricle" was first used by Braun in 1952 to describe the postmortem anatomy of a heart with complete dextroposition of the aorta, subaortic VSD, and pulmonary stenosis.[5] Five years later, another series of postmortem examinations described four cases of what were termed "double outlet right ventricle." The first recognition of DORV on a living patient was made the same year at Mayo Clinic at the time of surgical correction.[6]

During the decades that followed, the complex spectrum of anatomic variations that could be classified as subgroups of DORV became apparent. The importance of distinguishing DORV from simple VSD prior to attempting surgical intervention was emphasized by Engle and Steinberg.[7] Neufeld was the first to suggest clinicopathologic subsets of DORV when he stratified patients into those with or without pulmonary stenosis.[8] In the same original manuscript that distinguished patients without pulmonary stenosis,[8] he described the location of the VSD relative to the aorta and pulmonary artery (PA). This seminal work was carried forward by Lev when he classified the VSD relative to their position to the subarterial outlets: subaortic, subpulmonary, doubly-committed, and non-committed.[1] The importance of the spacial relationship of the great vessels to each other was also highlighted.[9–11] Although the Taussig-Bing heart was physiologically more similar to TGA with VSD,[12] it was Neufeld who recognized that the Taussig-Bing heart was an anatomic subset of DORV.[13] Mayo Clinic surgeons were the first to report surgical correction of the Taussig–Bing heart,[14] and intraventricular tunnel repair of this disorder.[15]

## Embryology

There are two theories that attempt to describe the cono-truncal abnormalities that result in the development of DORV. Lev has proposed that DORV results when there is an abnormal spiraling septation of the aorta from the PA that is more than Fallot's tetralogy but less than transposition.[16] Alternatively, Van Praagh's theory proposed that conal underdevelopment results in the great arteries emerging from the RV in a side-by-side arrangement.[17]

## Classification

Based on the spatial relationship of the VSD to the semilunar valves, DORV can be anatomically classified as subaortic, subpulmonary, doubly-committed, or remote.[1] It should be noted, however, that the pathophysiology and type of surgical repair are influenced not only by the relative location of the VSD to the semilunar valves, but also by the relationship of the great arteries to each other, and any associated abnormalities. Because there is no absolute correlation between the commitment of the VSD to the great arteries and the surgical approach,[18,19] a nomenclature system that defines four types of DORV based on clinical presentation and treatment has been adopted by the STS-EACTS.[2] The four types are: (1) VSD-type, (2) Fallot-type, (3) TGA-type, and (4) DORV with non-committed VSD. This system offers the advantage of uniformity to DORV nomenclature which allows an accurate and reproducible pediatric cardiac surgery database, resulting in reliable and meaningful outcome studies for the variety of surgical procedures available.

## Ventricular Septal Defect

DORV is, for practical purposes, always associated with a VSD. Rarely is DORV not associated with an interventricular communication,[20] and this anatomic rarity most likely represents spontaneous closure of a preexisting VSD. The most well known classification of DORV is based on the relative position of the VSD to the arterial outlets.[1] Most often, the VSD is located between the anterior and posterior limbs of the trabecula septomarginalis (TSM) (Fig. 71-1), and as such can be described as "committed."[21] The attachment of the infundibular septum to either the anterior or posterior limb predicts which great artery is related to the VSD. Sub-aortic VSD is associated with the infundibular septum being attached or aligned with the anterior limb of the TSM. Conversely, posterior limb alignment of the TSM with the infundibular septum results in a subpulmonary VSD. The infundibular septum is absent or markedly attenuated in cases of doubly-committed VSD. The non-committed VSD is away from the semilunar valve(s) and it has been proposed that this distance be greater than the diameter of the aortic valve.[22] The noncommitted VSD is located in the inlet septum (atrioventricular (AV) canal defect or muscular) or the trabecular ventricular septum. The majority of VSDs in DORV are unrestrictive, but restrictive VSDs may be seen in approximately 10 percent of patients. Although restrictive VSDs are diagnosed preoperatively in approximately 1.6 percent, an additional 11 percent of patients require VSD enlargement at the time of repair to prevent subaortic obstruction.[6,19] Multiple VSDs can be seen in 13 percent, and it is extremely rare for no VSD to be present. In the absence

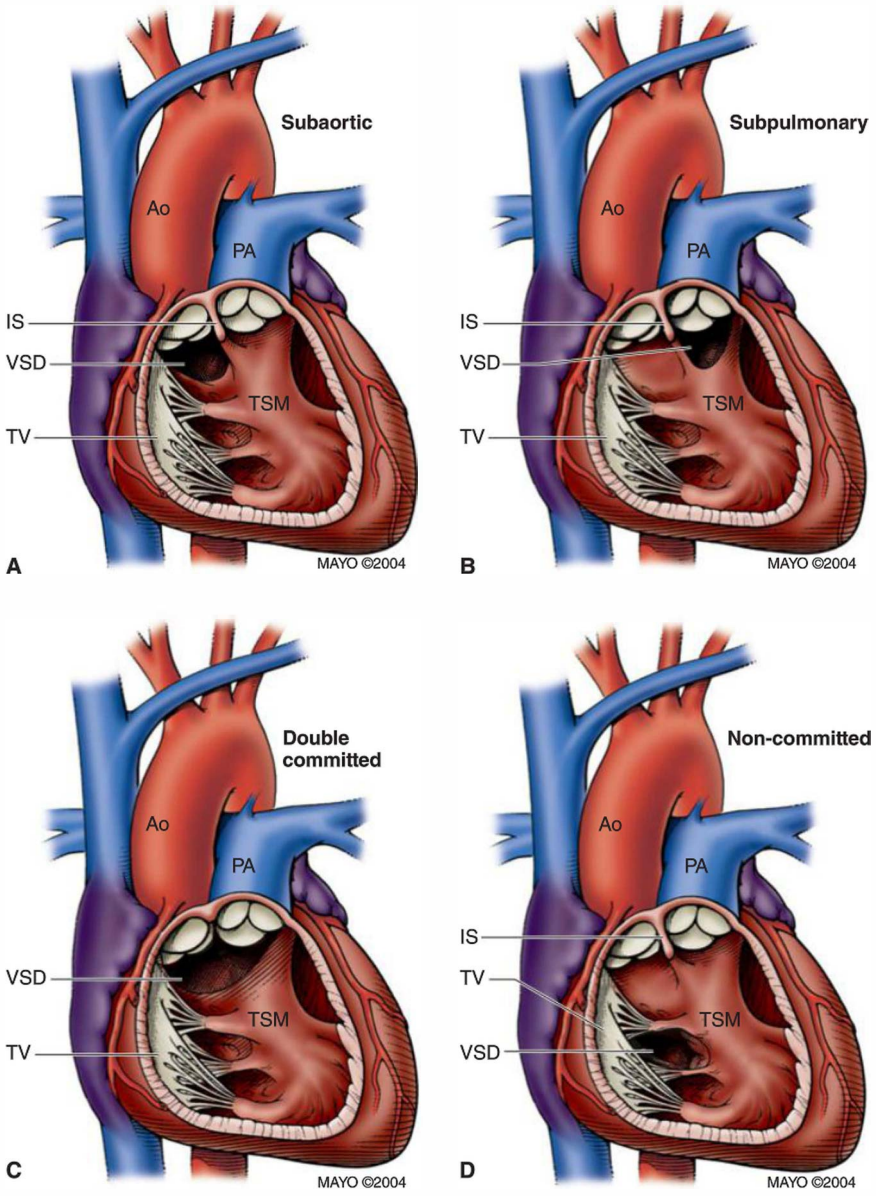



**FIGURE 71-1** **A.** Diagram illustrating double outlet right ventricle (DORV) with subaortic ventricular septal defect (VSD). **B.** Diagram illustrating DORV with subpulmonic VSD. **C.** Diagram illustrating DORV with doubly committed VSD. **D.** Diagram illustrating DORV with noncommitted VSD. Ao, aorta; PA, pulmonary artery; TSM, trabecula septomarginalis; TV, tricuspid valve; IS, interventricular septum. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

of a VSD, there is an ASD, which serves as left-to-right shunt. In this situation, the LV is usually hypoplastic.[2]

## SUBAORTIC VSD

This is the most common type of VSD and occurs in approximately 50 to 55 percent of patients undergoing repair of DORV. The VSD is unrestrictive. Bilateral coni are present in 77 percent of patients and a subpulmonary conus is present in 23 percent (Table 71-1).[22] The length of the conus determines the distance of the VSD from the aortic valve. Due to the relationship of the infundibular septum being aligned with the anterior limb of the TSM, the subaortic VSD is located in a posterior position in the ventricular septum

**TABLE 71-1: Relationship of VSD and Conus Pattern in DORV**

| | Type of Conus | | | |
|---|---|---|---|---|
| **Position of VSD** | **Bilateral (%)** | **Subaortic (%)** | **Subpulmonary (%)** | **Absent (%)** |
| Subaortic | 77 | 0 | 23 | 0 |
| Subpulmonary | 45 | 55 | 0 | 0 |
| Doubly committed | 67 | 0 | 0 | 33 |
| Non-committed | 50 | 50 | 0 | 0 |

Data based from Green Lane Hospital of 42 autopsy specimens and adapted from Kirklin JW, Barratt-Boyes BG. Double outlet right ventricle. In: Kirklin JW, Barratt-Boyes BG (eds). *Cardiac Surgery*, 3rd ed. New York: Churchill Livingston, 2003:1509–1539.

(Fig. 71-1A). In the presence of aortic–mitral fibrous continuity (i.e., absent subaortic conus; the left cusp or the base of the anterior leaflet of the mitral valve forms the posterosuperior margin of the VSD) the VSD is termed juxta-aortic. Individuals with a subaortic VSD have a relatively normal pattern of circulation.

### SUBPULMONIC VSD

This type of VSD is often seen in the Taussig-Bing anomaly. This VSD is located in a more anterior position in the ventricular septum since the posterior limb of the TSM is rotated and aligned with the infundibular septum (Fig. 71-1B). Pulmonary stenosis is usually absent and the VSD is unrestrictive. A subpulmonary VSD is present in approximately 30 percent of patients with DORV undergoing surgical repair.[6,19] As with the subaortic VSD, the length of the pulmonary conus determines the distance of the VSD from the pulmonary valve. In this situation, the conus forms the anterosuperior margin of the VSD. The absence of subpulmonary conus results in pulmonary–mitral and occasionally pulmonary–tricuspid continuity. This results in the VSD being juxtapulmonary. Individuals with a subpulmonary VSD have a transposition-like circulation because the LV blood is directed to the PA.

### DOUBLY-COMMITTED VSD

This type of VSD is seen in 3 to 10 percent of surgical series.[23] The VSD is usually large due to attenuated or absent infundibular septum. The semilunar valves form the superior border while the limbs of the TSM form the anterior, inferior and posterior margins (Fig. 71-1C).

### NONCOMMITTED VSD

This type of VSD is remote from the semilunar valves and is seen in 3 to 20 percent of surgical series.[22] Most are associated with DORV and complete AV septal defects. Straddling of the AV valve may be present with this type of VSD (Fig. 71-1D).

## Relationship of the Great Arteries

The relationship of the great arteries at the level of the semilunar valves in DORV can be grouped into two broad categories: (1) spiraling and (2) parallel. Spiraling great arteries is the normal anatomic relationship with the aortic trunk positioned posterior and to the right of the pulmonary trunk; this is the most common great vessel relationship in DORV.[2] When the great arteries are parallel, the aortic trunk is in a more anterior position relative to the pulmonary trunk. There are multiple degrees of variability in the anteroposterior relationship between aortic trunk and pulmonary trunks. In general, however, this relationship can be broken down into the following: (1) aorta located to the right and side-by-side with the PA (Taussig–Bing), (2) aorta located to the right and anterior to the PA (D-TGA), and (3) aorta located anterior and to the left of the PA (L-malposition).

It must be noted that the relationship of the great arteries and the type of VSD present are independent of each other. In general terms, however, spiraling and L-malposition of the great arteries are most commonly associated with a subaortic VSD. Side-by-side (parallel) great arteries are most often associated with a subpulmonic VSD.[2]

## Other Cardiac Anomalies

Associated cardiac anomalies are common with DORV, and almost any type of congenital cardiac anomaly can be present. At the Mayo Clinic, 179 patients with a diagnosis of DORV were operated on between 1972 and 1992, and 87 (48.6 percent) had concomitant congenital anomalies. Table 71-2 shows the concomitant anomalies present in this series. ASD was the most common associated anomaly, followed by persistent left SVC and coronary artery anomalies. Multiple VSDs were seen in approximately 12 percent of patients and are a risk factor for early mortality.[24] Coarctation of the aorta is a commonly associated anomaly in approximately 50 percent of patients with the Taussig–Bing form of DORV.[25]

Overriding and/or straddling of the AV valve apparatus may be present in DORV, making biventricular repair difficult. Straddling of the right AV valve may permit a biventricular

**TABLE 71-2: Concomitant Congenital Cardiac Anomalies in 179 Patients Undergoing Repair for DORV (Exclusive of Pulmonary Stenosis) at the Mayo Clinic From 1972 to 1992**

| | Number | Frequency (%) |
|---|---|---|
| ASD | 99 | 55 |
| Persistent L SVC | 34 | 19 |
| Coronary anomalies | 28 | 16 |
| Multiple VSDs | 22 | 12 |
| Nonconfluent PA | 21 | 12 |
| Situs inversus | 18 | 10 |
| PDA | 18 | 10 |
| Right aortic arch | 16 | 9 |
| AV discordance | 5 | 3 |
| Common atrium | 5 | 3 |
| Coarctation | 6 | 3 |
| AV canal | 6 | 3 |
| Mitral stenosis | 4 | 2 |
| TAPVC/PAPVC | 3 | 2 |
| Unroofed coronary sinus | 1 | 1 |

Adapted from unpublished data.

repair.[26] Significant overriding of the right AV valve may result in a small inlet portion of the RV after VSD closure and a concomitant bidirectional cavopulmonary shunt may be necessary.[27] Left AV (mitral) valve anomalies include mitral atresia, parachute valve, straddling, and supravalvular stenosing ring.

Pulmonary stenosis occurs commonly in DORV, particularly in those cases with subaortic and doubly-committed VSDs. The stenosis is most often at the level of the infundibulum.

## Coronary Artery Anatomy

The coronary artery anatomy in DORV is predominantly the normal pattern.[28] However, anomalous coronary patterns can be seen in up to 16 percent of patients undergoing operation. The most common abnormality is anomalous origin of the left anterior descending artery from the right coronary artery. This pattern is typically seen in the subgroup of DORV with subaortic VSD and right ventricular outflow tract obstruction (RVOTO).[29] Coronary arterial patterns that are seen with transposition of the great arteries are also present in patients with DORV.

## Conduction Tissue

The AV node and His bundles follow pathways that are specific for the type of AV connections. In AV concordance, the VSD is usually perimembranous (conoventricular) and the conduction tissue is along the posterior-inferior border of the defect. In the presence of AV discordance, the conduction pathways are anterior and adjacent to the PA.

# CLINICAL FEATURES

## Epidemiology

DORV is a rare congenital cardiac anomaly. Its frequency is approximately 0.09 per 1000 births. There is no racial or gender predominance.[30,31]

## Pathophysiology and Clinical Manifestation

### SUBAORTIC VSD

The position of the infundibular septum and the presence of RVOTO determine the clinical presentation. Anterior deviation of the infundibular septum producing RVOTO presents with cyanosis, similar to tetralogy of Fallot. Concomitant pulmonary stenosis may be present. Other findings that can be seen as a result of RVOTO include failure to thrive, dyspnea on exertion, squatting and polycythemia.

Management is similar to that of tetralogy of Fallot. In the absence of RVOTO, the clinical presentation is like that of a large VSD with heart failure being the presenting symptom.

### SUBPULMONARY VSD

Clinical presentation is usually cyanosis due to unfavorable streaming of deoxygenated blood into the aorta and oxygenated blood into the PA via the subpulmonary VSD. This presentation is very similar to that of patients with D-TGA. Subaortic stenosis may be present in up to 35 percent of patients with Taussig–Bing anomaly.[25] Concomitant coarctation or arch hypoplasia may occur in up to 50 percent of infants with DORV and subpulmonary VSD. Patients are seen in early infancy with cyanosis, heart failure, failure to thrive and frequent respiratory infections. High pulmonary blood flow in this subgroup of DORV results in pulmonary vascular obstructive disease at an early age if surgical correction is not undertaken.

### DOUBLY-COMMITTED VSD

This lesion is uncommon and presentation depends on the presence of favorable or unfavorable streaming. Pulmonary stenosis may also be present.

### REMOTE VSD

Clinical presentation is similar to patients with single ventricle. Oxygen saturations are usually that of complete mixing due to the remoteness of the VSD from the great arteries. Pulmonary blood flow may be balanced, increased or decreased.

# PHYSICAL EXAMINATION

There are no specific findings on physical exam that are pathognomonic of DORV. Patients in heart failure can present with tachypnea and failure to thrive, while cyanosis is seen in patients with inadequate pulmonary blood flow.

## DIAGNOSTIC STUDIES

### Electrocardiography

There are no electrocardiography (ECG) findings that are pathognomonic for DORV. There are, however, certain ECG abnormalities that can be seen in DORV (Fig. 71-2). The most common abnormality seen is RV hypertrophy and right axis deviation. This is a result of high RV pressures. LV hypertrophy can be seen in the presence of a restrictive VSD or from volume overloading in the presence of high pulmonary blood flow as can be seen in DORV with subpulmonic VSD (Taussig–Bing anomaly). Right atrial enlargement is commonly seen with pulmonary stenosis. In contrast, left atrial enlargement is seen in the absence of pulmonary stenosis or when functional mitral stenosis is present. Other ECG abnormalities include first-degree AV block and left axis deviation due to posterior displacement of the conduction tissue.

### Chest X-Ray

Variable chest x-ray findings can be associated with DORV. Patients with pulmonary stenosis will have diminished pulmonary vascular markings. In contrast, patients with high pulmonary blood will show increased pulmonary markings. Patients presenting late with pulmonary vascular obstructive disease usually have diminished pulmonary vascular markings and prominent central pulmonary arteries. Cardiomegaly can be present. DORV with RVOTO (i.e., TOF physiology) may have RV hypertrophy and an upwardly turned apex of the cardiac silhouette. LV hypertrophy and enlargement, which may be seen in the presence of an unrestrictive VSD may have a downwardly turned and displaced apex below the diaphragm.

### Echocardiography

Transthoracic echocardiography is the imaging technique that is most commonly used for making the diagnosis of DORV. Transesophageal echocardiography is utilized for more complex abnormalities of the AV valves (i.e., overriding and straddling). Diagnosis is established by demonstrating both great arteries predominately arising from the anterior RV, and VSD as the sole outlet of the LV. Echocardiography can also delineate aortic–mitral fibrous discontinuity. Concomitant cardiac anomalies (i.e.,

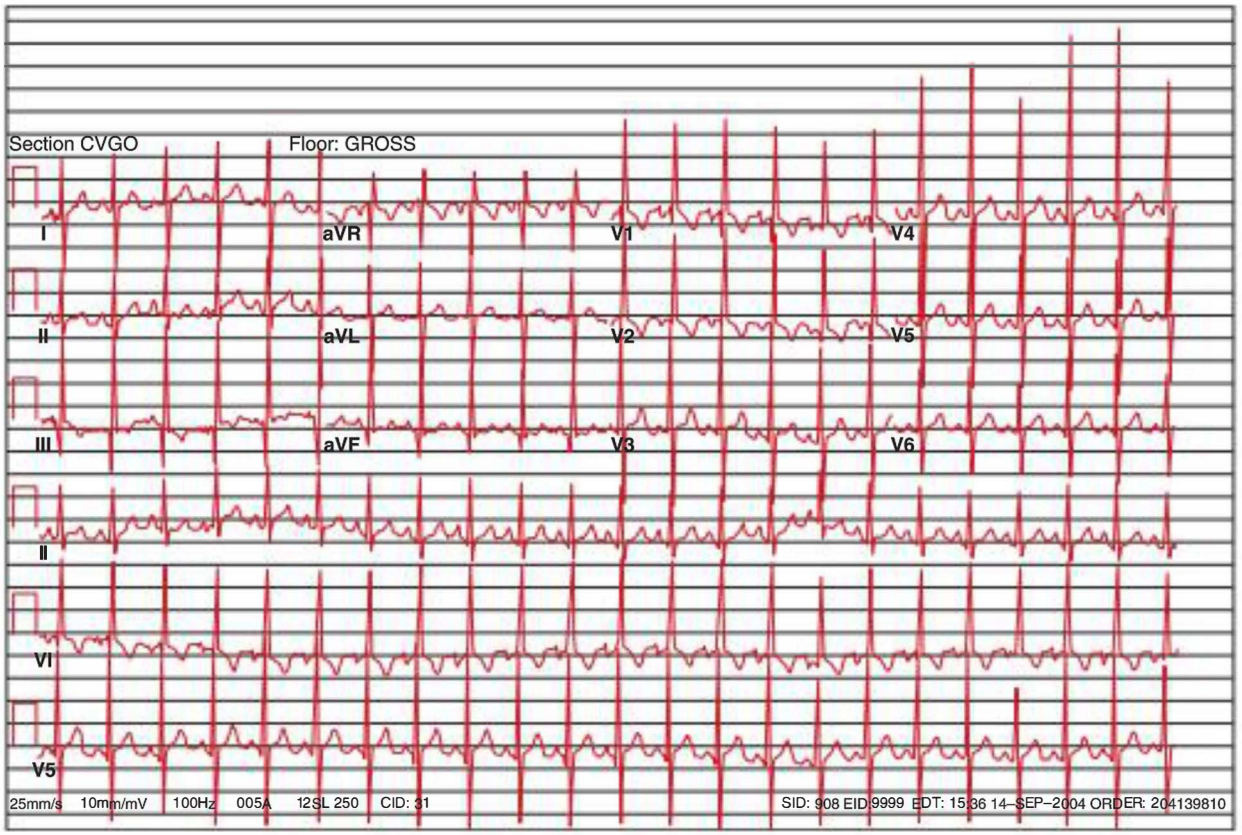



**FIGURE 71-2** Electrocardiograph of 6-month-old patient with DORV and subaortic VSD, exhibiting some of the features that can be seen with this anomaly: normal sinus rhythm with biatrial enlargement, right ventricular hypertrophy and right axis deviation.

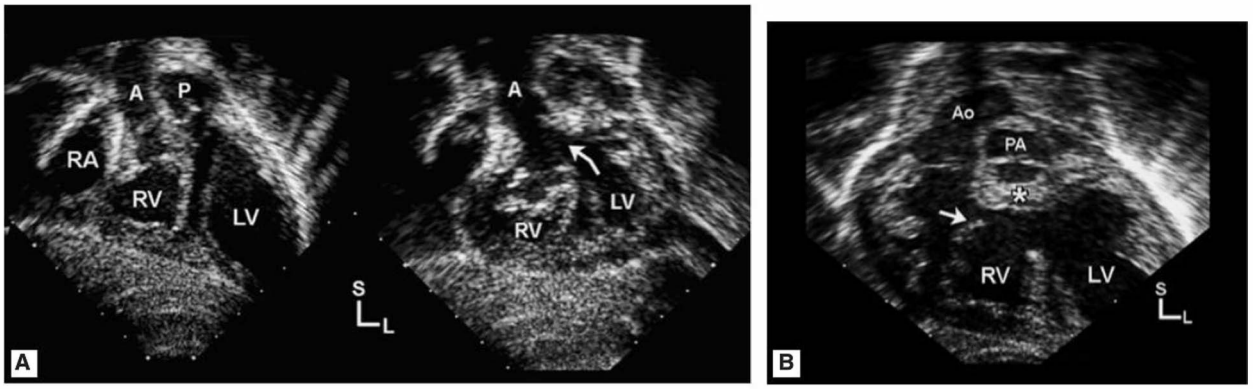



**FIGURE 71-3** **A.** Transthoracic echocardiogram (ECHO) in patient with double outlet right ventricle with subaortic VSD. Left image: Subcostal four-chamber view with anterior angulation demonstrates both great arteries arising from the right ventricular outflow tract (RVOT) with aorta (A) to the right and pulmonary artery (P) to the left. Right image: Slight posterior angulation of the scan plane reveals that the ventricular septal defect (VSD) (arrow) is closely related to the aorta. There is infundibular muscle interposed between the VSD and the pulmonary the pulmonary valve. There is no pulmonary or subpulmonary stenosis and no important structures or valve attachments lying between the VSD and the aortic valve. Repair in this situation requires placement of an intraventricular tunnel to direct left ventricular outflow across the VSD toward the aorta and allowing the right ventricle to eject anteriorly to the patch directly into the pulmonary artery. **B.** Transthoracic echocardiogram illustrating double outlet right ventricle with remote VSD. Subcostal four chamber view with anterior angulation demonstrates both great arteries arising from the RVOT. Note, however, that the semilunar valves are relatively further away as compared to the ECHO shown in A. The pulmonary valve is to the left and is separated from the VSD by a thick wall of malposed infundibular septum (asterisk). The tricuspid valve has an outlet attachment that is positioned between the VSD and the aortic valve (arrow). Simple septation in this case is not possible. The three options for complete repair here would be to: (1) perform a complex intraventricular tunnel (multiple patch technique) and tricuspid valve replacement; (2) arterial switch operation with resection of the leftward portion of the malpositioned infundibular septum; and (3) treat this complex anatomical DORV variant as a functionally univentricular heart and channel the patient down a Fontan palliation strategy.

coronary artery patterns, coarctation, etc.) are usually readily noted by echocardiography. Usually echocardiography is the only diagnostic modality required in an infant for establishing the appropriate plan of management. Figure 71-3 illustrates some of the characteristic views by echocardiography in making the diagnosis of DORV. Additional diagnostic techniques are usually required in older children and adults.

## Cardiac Catheterization

Cardiac catheterization may be required to determine hemodynamics for suitability of repair, exclude pulmonary vascular obstructive disease and to determine coronary artery anatomy.

## Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) provides complementary information about associated intracardiac defects and the relationship of the aorta and PAs. In addition, MRI can provide a 3-dimensional relationship of the cardiac chambers and arrangement of the great vessels and coronary arteries, as well as an accurate assessment of left and RV size and function. MRI may be helpful in predicting feasibility of biventricular repair in DORV hearts with non-committed VSDs.[32]

# SURGICAL THERAPY

In 1957, Kirklin performed the first repair of DORV in a child at the Mayo Clinic. This technique involved an intraventricular tunnel to establish LV–aortic continuity via a subaortic VSD.[6] Since that time, many surgical procedures have been developed to repair some of the more complex anatomical variations seen with DORV.[33–37] The optimal surgical approach is tailored to the specific anatomy. Complete anatomical repair is the goal when feasible. This includes establishing continuity of the LV with the systemic circulation, the RV to the pulmonary circulation and VSD closure.

A palliative operation prior to complete repair may be required, and is undertaken in 42 to 75 percent of patients with DORV.[24,33,34] Furthermore, approximately 25 percent will undergo more than one palliative operation, thus illustrating the complexity of this anomaly. Palliative operations have included systemic to PA shunts, PA banding, and repair of other anomalies such as coarctation. Anatomical anomalies precluding complete repair include ventricular hypoplasia, straddling or overriding of the atrioventricular valves, multiple VSDs, pulmonary obstructive vascular disease and other associated complex cardiac anomalies.

It is helpful to the surgeon to categorize DORV into four groups, which helps in guiding the appropriate surgical management:

1. Subaortic or doubly-committed VSD and RVOTO—TOF-type
2. Subpulmonary VSD—TGA-type

3. Subaortic or doubly committed VSD without RVOTO—VSD-type
4. Noncommitted VSD with or without RVOTO

## Subaortic or Doubly Committed VSD Without RVOTO (VSD Type)

The VSD is usually exposed through a longitudinal right ventriculotomy with care taken to avoid injury to large conal branches or the left anterior descending artery. A right atrial approach can also be performed. However, it is difficult to assess proper alignment of the intraventricular tunnel from the VSD to the aorta with this approach. After the right ventriculotomy is made, the size and location of the VSD is established, particularly noting whether the VSD abuts the tricuspid valve or has a rim of muscle along its posterior border. The diameter of the VSD must be at least the diameter of the aortic annulus to prevent outflow tract obstruction to the aorta. If the VSD is restrictive, it is enlarged by resecting a wedge of muscle in an antero-superior direction. Obstructing muscle bundles of the RV and a small portion of the infundibular septum are often excised for proper alignment of the patch, which is shaped like a tunnel. RVOTO is a potential complication of this procedure. This problem is avoided by establishing that the distance between the tricuspid annulus and the pulmonary annulus is at least the diameter of the aortic annulus. This can be assessed preoperatively by subxiphoid views on echocardiography and by intraoperative assessment. The VSD patch material used is often a Sauvage Dacron patch (USCI Sauvage filamentous Dacron fabric, C.R. Bard, Inc, Bellerica, MA.), Gore-Tex (W.L. Gore and Assoc., Inc, Flagstaff, AZ.), or a tailored Dacron tube graft. The patch is sewn to channel the flow of blood from the LV across the VSD to the aortic annulus. It is important to note that the patch is not flat, but rather an opened tube or tunnel, thus providing an unobstructive channel between the VSD and the aorta. Superiorly, the patch is sewn to the aortic annulus. Posteroinferiorly, the suture line is deviated away from the edge of the VSD to avoid injury to the conduction tissue. Posteriorly, the patch is sewn to the base of the septal leaflet of the tricuspid valve. If muscle interposes the tricuspid annulus and VSD then the VSD repair sutures can be placed in this muscle without damaging the conduction tissue (Fig. 71-4). The right ventriculotomy is closed with a patch to avoid RVOTO created by the intraventricular tunnel.

Complete intraventricular tunnel repair is performed within the first 6 months of life because of the increased risk of developing pulmonary vascular obstructive disease. In previous years, initial palliation with a PA band followed by an intraventricular tunnel and debanding in early childhood was performed.

## Subaortic VSD and RVOTO (TOF Type)

The repair of this anomaly is similar to repairs described ifor TOF (see Chapter 68). Exposure is usually accomplished via a right ventriculotomy; however, exposure of the VSD can be

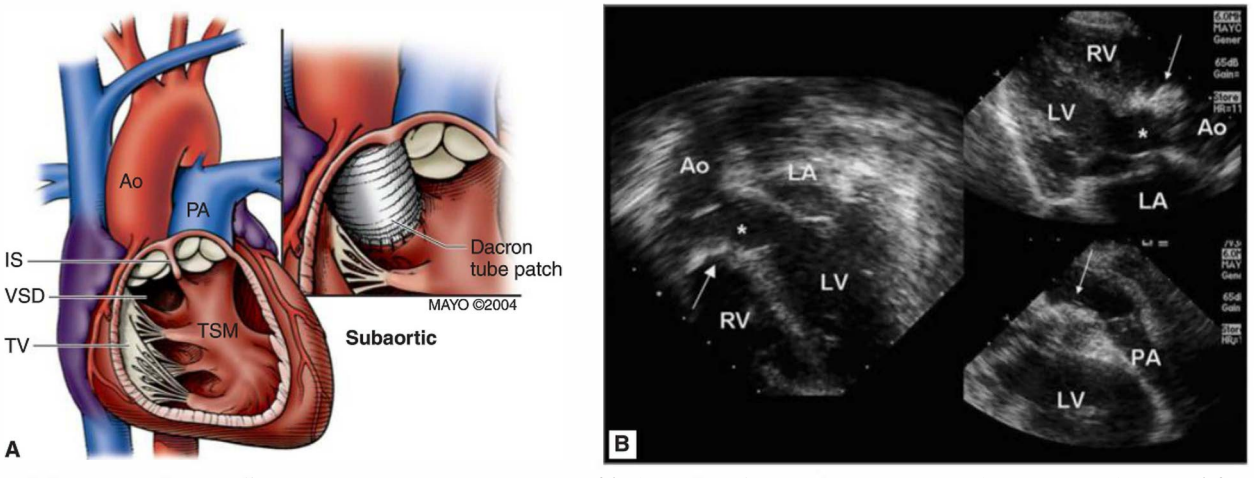



**FIGURE 71-4** **A.** Diagram illustrating intraventricular tunnel repair of double outlet right ventricle (DORV) with subaortic ventricular septal defect (VSD). Left ventricular ejection is directed via the VSD to the aorta. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.) **B.** Postoperative transthoracic echocardiogram illustrating repair in a patient with DORV and subaortic VSD with no postoperative left ventricular outflow tract and right ventricular outflow tract obstruction. The left panel is an anteriorly angulated apical view illustrating deviation of the VSD patch (subaortic VSD) in order to channel flow from the VSD to the aorta. The arrow points to the right ventricular (RV) surface of the VSD patch. The asterisk indicates the pathway from the left ventricular (LV) to the aortic valve created by the patch. The upper right panel is a parasternal long-axis image in the same patient. Again, the arrow points to the RV surface of the patch and asterisk indicates the pathway from the LV to the aortic valve created by the patch. The lower right panel is a modified parasternal view focused on the long axis of the main pulmonary artery. The RV outflow has been deviated anterior to the patch (arrow), but remains widely patent.

obtained via the transatrial approach. The os of the infundibulum is resected to enlarge the right ventricular outflow tract (RVOT). The VSD is closed using the tunnel technique described above. The right ventriculotomy is closed with a patch to prevent RVOTO. An anomalous coronary artery crossing the RVOT can limit the ventriculotomy, resulting in inadequate relief of RVOTO. In this situation, a valved extracardiac conduit from the RV to PA can be used. In the current era, most centers would perform complete repair in the first year of life. Alternatively, palliation with a shunt can be performed if surgical treatment is required in the first 2 to 3 months of life.

## Subpulmonary VSD (Taussig–Bing Type)

The operation of choice for DORV with subpulmonary VSD and no RVOTO (i.e., Taussig–Bing anomaly) is the arterial switch operation and patch closure of the VSD, directing blood flow from the LV to the pulmonary (neoaortic) valve (Fig. 71-5). Details of the arterial switch operation are described in Chapter 74. Closure of the VSD can be performed via the right atrium, RV or the aortic root (neopulmonary artery) depending on the location of the VSD.

Results of the arterial switch operation for this anomaly has been excellent, and the operative mortality for this form of DORV has significantly decreased in recent years.[37]

Intraventricular tunnel repair techniques such as the Kawashima operation are performed less commonly for patients with Taussig-Bing anomaly.[38] Increasing expertise with the arterial switch operation has made the Kawashima repair less appealing.

Concomitant aortic arch hypoplasia can be present with Taussig–Bing hearts and should be addressed as a single-stage complete repair. In the presence of arch hypoplasia, there is a high likelihood of hypoplasia of the RVOT leading to clinically important infundibular obstruction. As such, RVOT obstruction should always be evaluated in the presence of arch hypoplasia.

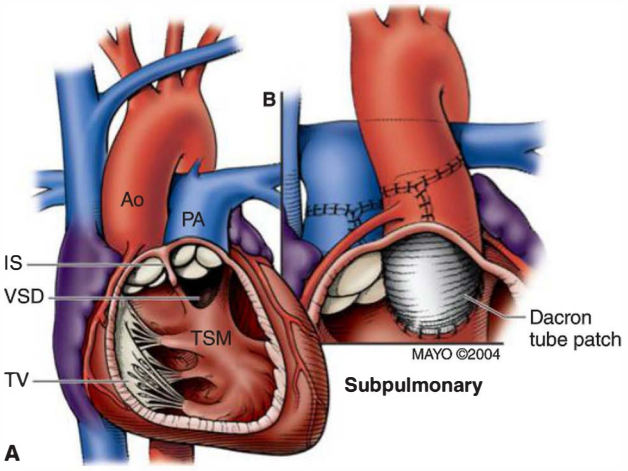



**FIGURE 71-5** Diagram illustrating arterial switch operation and tunneling of LV flow through the VSD to the neoaorta for Taussig–Bing anomaly. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

The REV operation (*réparation à l'etage ventriculaire*) introduced by Lecompte is yet another intraventricular repair designed for patients in whom an arterial switch and simple intraventricular tunnel repair of the VSD are not feasible. This situation arises when there is coexisting LV outflow tract obstruction, that is, pulmonary stenosis. In this operation the LV outflow is directed to the aorta and the pulmonary trunk is transected with the distal segment directly anastomosed to the RV.[39,40]

## Doubly-Committed VSD

This anatomy is uncommon. When present, repair is usually accomplished in the first 6 months of life. Closure of the superior aspect of the VSD may be challenging because of the absence of the infundibular septum. Enlargement of the VSD is performed as needed and as described above. If the VSD is more closely related to the PA, then arterial switch operation as described for the Taussig–Bing anomaly is preferred.

## Non-committed VSD

Surgical repair in this group is complex and challenging. Despite the challenges faced with the long-term results of the Fontan operation,[41] many groups continue to pursue univentricular palliation.[42] Typically, this strategy involves placement of a PA band during the neonatal period. A bidirectional cavopulmonary shunt is performed at 4 to 6 months of age. The Fontan procedure is then performed between 18 months and 4 years of age.

The Fontan procedure has undergone many modifications and, presently, medium-to-late term results are quite favorable.[24] As a result, some have advocated that the more complex anatomical variants of DORV be channeled toward a single ventricle physiological track.[35] Brown et al. in their 20-year experience in treating DORV performed modified Fontan operations in 26.6 percent of patients with DORV. In addition to remote VSD, indications for Fontan type operations have included complex anomalies such as straddling AV valves, AV septal defects or hypoplastic LV, or a combination of AV septal defects and hypoplastic ventricle, atrial isomerism, multiple VSDs, and major PA anomalies including atresia, slings, and discontinuous branch pulmonary arteries. Early morality when Fontan-type operations are performed has been shown to be approximately 5 percent in this complex group of patients.[33]

Although a biventricular repair is desirable in the presence of two normally functioning ventricles and AV valves, the complexity of the intracardiac repair and tunnel can be associated with high early mortality.[6] The distance between the noncommitted VSD and the aorta necessitates a long

prosthetic intracardiac baffle. This can result in impaired function of either the tricuspid or pulmonary valves or the creation of an akinetic portion of the LV. Another obstacle to the two-ventricle repair is the subaortic obstruction caused by the baffle as a result of somatic growth. Others have reported a multiple patch technique to create the tunnel between the VSD and aorta.[43] One possible solution is tunneling the VSD to the pulmonary infundibulum followed by an arterial switch.[36]

There are few data describing the results of intracardiac repair of non-committed VSD type DORV. Of 10 patients undergoing rerouting of the VSD to the PA followed by arterial switch, there was only 1 postoperative death. At 20 months, the remaining nine survivors were in NYHA class I, in sinus rhythm, and had no subaortic gradient greater than 15 mm Hg.[36] Of 7 patients with tunneling of the VSD to the aorta,[44] 70 percent of these patients required VSD enlargement and 60 percent required a subaortic resection of the conal septum.[45] Two patients with VSD enlargement required a pacemaker. There was one postoperative death in a patient who developed mediastinitis. There was one late reoperation in a patient with non-committed VSD-type DORV who underwent VSD–PA baffle and an arterial switch operation.

## PALLIATIVE OPERATIONS

Palliative operations are less frequently performed in the current era due to lower mortality rates demonstrated with complete repair in neonates and infants. Furthermore, recent series have shown that patient age and weight do not adversely impact mortality.[33,34] However, these studies were undertaken in centers that perform a large number of operations in neonates and infants. Many reported surgical series continue to demonstrate between 42 and 75 percent of patients having had an initial palliative operation, most being a modified Blalock-Taussig shunt.[6,22] This may reflect, in part, that many patients were operated on in an earlier era. This percentage will continue to decrease as results of complete repair during infancy continue to improve.

## OUTCOME/PROGNOSIS

Results of complete repair for DORV have been reported in large contemporary series[24,33,36,46] and early mortality has been shown to range from 2.6 to 9 percent. In general, late outcome is determined by anatomy and postrepair physiology.

Patients with DORV similar to tetralogy of Fallot, have results similar to tetralogy of Fallot. When repair requires the use of an RV-to-PA conduit, repeat operation(s) for conduit replacement are required. The REV procedure (PA directly attached to the RV) may lessen the need for reoperation,[47] but may occur at the expense of RV dilatation and subsequent RV failure.

Patients undergoing arterial switch operation have excellent late survival. In contrast to simple transposition, the incidence of neoaortic valve regurgitation is more common and may require the need for reoperation for valve repair or replacement.[48]

Subaortic obstruction is a complication that can be seen both early and late in patients who have undergone complete repair for DORV. This complication is a result of intracardiac tunneling of the VSD to the aorta. Late development of subaortic obstruction results from protrusion of the inferior rim of the tunnel into the LVOT or from fibrous tissue growth below the aortic valve.[49] The risk of this complication can range from 5 to 50 percent depending on the individual anatomy. Treatment of subaortic obstruction is surgical and involves an extended septoplasty (Fig. 71-6) and subaortic resection of fibrous tissue.

Brown et al. reported a 20-year experience in 124 patients. Survival at 15 years was 96 percent for simple intracardiac repairs, 90 percent for subpulmonary VSD, and 90 percent for straddling AV valves or hypoplastic ventricles. Freedom

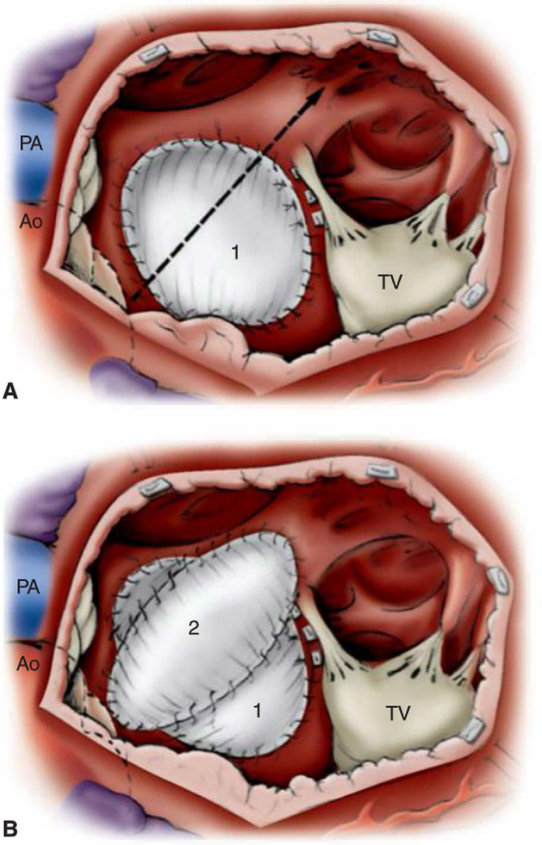



**FIGURE 71-6** Extended septoplasty for management of late subaortic obstruction following complete repair for DORV. **A.** Right ventriculotomy approach. The arrow illustrates the septal incision made through the patch and toward the apex (leftward). **B.** Following septal incision, a second patch is placed resulting in augmentation of the LVOT. (Reprinted with permission from Belli et al., *J Thorac Cardiovasc Surg* 1996;112:1570.)

from reoperation at 15 years was 87 percent for simple intracardiac repairs, 72 percent for subpulmonary VSD, and 100 percent for those with more complex intracardiac anatomy who underwent an arterial switch operation and VSD closure, thus avoiding a complex intracardiac tunnel repair.

Risk factors for early mortality have been variable and include aortic arch obstruction, AV septal defects, mitral stenosis/regurgitation, multiple VSDs and age less than 1 month.[24,33,34]

## CONCLUSIONS

In summary, DORV is a type of ventriculo–arterial connection whereby both great arteries arise from the RV. It is a form of complex congenital heart disease that can be associated with many other cardiac anomalies. The physiology and clinical presentation ranges from VSD-like physiology, to tetralogy of Fallot, to transposition, to single ventricle physiology. Understanding the physiology allows the proper surgical management strategy. Late results are favorable for most patients, although the potential need for reoperation remains.

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## DOUBLE OUTLET RIGHT VENTRICLE BOARD REVIEW QUESTIONS (CHAPTER 71)

1. Which is not a recognized type of DORV?
   A. VSD type
   B. Fallot type
   C. Mitral atresia type
   D. TGA type
   E. Noncommitted VSD type

2. Which is correct regarding the VSD in DORV?
   A. Subaortic VSD is the least common type.
   B. Bilateral coni are present in over 75 percent of patients with a subaortic VSD.
   C. A doubly committed VSD is associated with the Taussig–Bing heart.
   D. A subpulmonic VSD is associated with pulmonary stenosis and is restrictive.
   E. Noncommitted VSDs are associated with DORV and partial AV canal defects.

3. Which is true regarding clinical features of DORV?
   A. Anterior deviation of the infundibular septum and a subaortic VSD presents with cyanosis.
   B. Clinical presentation of a subpulmonary VSD is usually congestive heart failure.
   C. Subpulmonary VSDs are associated with arch hypoplasia in less than 10 percent of patients.
   D. A doubly committed VSD almost always presents with cyanosis.
   E. A remote VSD presents with cyanosis due to the distance from the PA.

4. Which of the following is correct regarding surgical repair of DORV?
   A. Complete intraventricular tunnel repair is performed after 1 year of palliation for subaortic or doubly committed VSD without RVOTO.
   B. Most centers will perform complete repair of subaortic VSD with RVOTO within the first year of life.
   C. The operation of choice for subpulmonary VSD without RVOTO is the atrial switch operation.
   D. Concomitant arch hypoplasia and Taussig–Bing heart is best treated with a two-stage repair.
   E. Noncommitted VSD is treated with simple patch closure of the VSD.

5. Which is true regarding outcomes after repair of DORV?
   A. Early mortality is 10 to 15 percent.
   B. The REV procedure reduces RV size over time.
   C. The incidence of neoaortic valve regurgitation after arterial switch for DORV is higher than after repair for simple transposition.
   D. AV septal defects are not a risk factor for early mortality.
   E. Subaortic obstruction occurs in less than 10 percent.

## ANSWERS

1. **Answer: C.** There is no mitral atresia type of DORV. The four types adopted by the STS and EACTS are VSD, Fallot, TGA, and noncommitted VSD.
2. **Answer: B.** Bilateral coni are present in over 75 percent of patients with a subaortic VSD. Subaoartic VSD is the most common type. Taussig–Bing anomaly is associated with a subpulmonic VSD. This form of VSD is typically unrestrictive and there is no pulmonary stenosis. Noncommitted VSDs are associated with DORV and complete AV canal defects.
3. **Answer: A.** Anterior deviation of the infundibular septum and a subaortic VSD presents with cyanosis due to RVOT obstruction. Clinical presentation of a subpulmonary VSD is usually also cyanosis. Subpulmonary VSDs are associated with coarctation or arch hypoplasia in up to 50 percent of patients. A doubly committed VSD has variable presentation due to streaming patterns. A remote VSD also has variable presentation due to the complete intracardiac mixing.
4. **Answer: B.** Most centers will perform complete repair of subaortic VSD with RVOTO within the first year of life. Complete intraventricular tunnel repair is performed

within the first 6 months for subaortic or doubly committed VSD without RVOTO. The operation of choice for the Taussig–Bing heart is arterial switch with patch VSD closure. Concomitant arch hypoplasia and Taussig–Bing anomaly is best treated with a single repair strategy. Noncommitted VSD is a complex anomaly and best individualized.

5. **Answer: C.** The incidence of neoaortic valve regurgitation after arterial switch for DORV is higher than after arterial switch for simple transposition. Early mortality rates range from 3 to 9 percent. The REV procedure can result in RV dilation and failure. AV septal defects are a risk factor for early mortality. Subaortic obstruction occurs in up to 50 percent of patients.

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# Truncus Arteriosus

*Tara Karamlou*
*D. Michael McMullan*
*Gordon A. Cohen*

**KEY CONCEPTS**

- Epidemiology
  - Truncus arteriosus is a rare cyanotic cardiac malformation with an incidence of 0.07 per 1000 live births (1.1 percent of all cardiac anomalies), with 40 percent of patients disclosing 22q11 deletion on genetic testing. There is also a variable phenotypic association with DiGeorge syndrome and craniofacial defects.
- Morphology
  - A single truncal valve usually overrides a large ventricular septal defect. The different classification schemes are based on the origin of the pulmonary arteries (PAs) (from truncus, ductus arteriosus, or descending aorta), the association of aortic arch interruption, and ventricular septal defects.
- Pathophysiology
  - Typically, there is intracardiac mixing (atrial and/or ventricular septal defect) with pulmonary over-circulation and, if interrupted aortic arch (IAA) is present, features of duct-dependent distal aortic perfusion. If untreated, chronic pulmonary vascular changes ensue, leading to fixed pulmonary hypertension.
- Clinical features
  - Presentation is in the neonatal period with pulmonary over-circulation and worsening symptoms as pulmonary vascular resistance falls. Hemodynamic collapse, acidosis, and lower body malperfusion are seen in patients with associated IAA and closure of the patent ductus arteriosus.
- Diagnosis
  - Echocardiography is usually all that is needed to proceed to surgical correction. Truncal anatomy, truncal valve morphology and function, location of the ventricular septal defect, and coronary anatomy are usually well defined echocardiographically. Additional diagnostic modalities include cardiac catheterization, computed tomography, and magnetic resonance imaging with three-dimensional reconstruction.
- Treatment
  - Complete repair in the neonatal period is standard treatment, following resuscitation and prostaglandin ($PGE_1$) infusion in newborns with IAA and ductal closure. Repair entails closure of the ventricular septal defect, truncal septation with reestablishment of continuity from the right ventricle (RV) to the PA with a valved conduit, and, if required, IAA and truncal valve repair. PA banding is currently very rarely performed in neonates and infants, in whom complete correction is contraindicated.
- Outcomes
  - In contemporary series, operative mortality ranges between 4 and 7 percent and is correlated to the reactivity of the pulmonary vascular bed and operative weight below 3 kg. Long-term prognosis is dependent on need for reintervention for truncal valve repair/replacement and structural failure of the RV-PA conduit.

## HISTORY AND EPIDEMIOLOGY

Truncus arteriosus (also termed common arterial trunk) is an unusual[1-4] developmental anomaly, characterized by incomplete conotruncal septation, leading to a common aortopulmonary trunk and ventricular septal defect. The disorder was first described by Wilson in 1798.[5] Initial surgical management consisted of palliative pulmonary artery (PA) banding; however, long-term survival associated with this treatment was poor. The first surgical repair was performed in 1962, when Behrendt and colleagues closed the ventricular septal defect and used a valveless conduit to

establish continuity between the right ventricle (RV) and the PA.[6] Complete repair of truncus arteriosus with a valved conduit was first reported by McGoon in 1967[7] and remains the procedure of choice for the majority of patients.

A recent prospective population-based study estimated the prevalence of truncus arteriosus to be approximately 0.07 per 1000 live births, representing 1.09 percent of all congenital cardiac malformations.[3,8] The incidence may be more than 3-fold higher in infants of diabetic mothers.[9] Twenty years ago, the 1-year mortality rate for corrected truncus arteriosus was estimated at 2.6 per 100,000 live births, representing 3.7 percent of all deaths due to congenital heart disease during that period.[10] Median 1-month mortality was 23 percent. With contemporary advancements in surgical technique and perioperative management, survival is likely higher. Without surgical correction, approximately 70 percent of infants die within the first 3 months of life,[11] whereas some individuals who are diagnosed later in life may survive for years without surgical intervention.[12–15] This subset likely represents those individuals with relatively balanced pulmonary-systemic circulations during infancy, and in whom severe pulmonary vascular obstructive disease inevitably develops.

## EMBRYOLOGIC DEVELOPMENT

The heart and great vessels develop from primitive mesoderm and neural crest cells. At approximately 20 days' gestation, blood islands of the cardiogenic plate coalesce to form the left and right endocardial tubes within the intraembryonic coelom (early pericardial cavity). The endocardial tubes fuse to become the bulbus cordis at approximately 23 days. The most cephalad portions of the bulbus cordis become the truncus arteriosus and conus cordis. During this period, the bulboventricular structures begin to rotate anteriorly and to the right to form the heart loop. At approximately 29 days, cono-truncal swellings begin to develop into distinct ridges. As these ridges grow, they fuse to form the truncal septum, which divides the aorta from the PA and the conal septum, becoming the supraventricular crest and the subpulmonic infundibulum. Spiral rotation along an axis similar to the heart loop separates the posterolateral aortic root from the more antero-medial PA root at approximately 37 days. Fusion of the conal septum with the endocardial cushions during this period establishes ventricular separation, with resultant left ventricle–aorta and RV–PA concordance.

Persistent truncus arteriosus results from incomplete or altered septation and rotation of components of the bulbus cordis. Morphogenetic patterning of the conotruncus, and eventual septation into a PA and aorta, involves initial migration of the dorsal and ventral neural crest cells followed by differentiation of these cells into vascular smooth muscle cells, in response to poorly characterized developmental cues.[16–18] Experimental ablation of these regions of the neural crest is associated with hypoplasia or aplasia of the thymus, thyroid, and parathyroid glands and persistent truncus arteriosus. Although the mechanisms by which neural crest cells regulate cono-truncal development have not been clearly elucidated, it is believed that alterations in neural crest cell migration may explain the association between cono-truncal malformations and cranio-facial defects such as those observed in patients with the DiGeorge syndrome. Recent experimental studies have implicated abnormalities in the family of GATA zinc-finger transcription factors, particularly GATA-6, which play critical roles in regulating morphogenetic patterning of the cardiac outflow tract and aortic arch during development.[19,20]

## GENETIC FACTORS

The genetic basis for persistent truncus arteriosus is likely multifactorial. An association between persistent truncus arteriosus and chromosome 22q11 deletion is well established. Chromosome 22q11 deletion affects approximately 700 infants annually in the United States and is present in 1.5 percent of patients with congenital heart defects[21] and in up to 40 percent of patients with truncus arteriosus.[22,23] Moreover, truncus arteriosus is present in approximately 10 percent of patients with chromosome 22q11 deletion.[24] In addition to cardiovascular malformations, chromosome 22q11 deletion has also been clearly linked to aplasia and hypoplasia of the thymus.[21,25,26] It is now recognized that 22q11 deletion syndrome encompasses the phenotypes previously described as DiGeorge syndrome and velocardiofacial syndrome. Because of these strong associations, genetic testing for chromosome 22q11 deletion in patients diagnosed with truncus arteriosus or thymic aplasia or hypoplasia is warranted. Recent evidence suggests that conditional inactivation of GATA-6 within neural crest cell derived smooth muscle cells results in cono-truncal defects including truncus arteriosus, interrupted aortic arch (IAA), and double-outlet RV.[19,27] Additional potential etiologic genetic alterations linked to truncus arteriosus include chromosomal duplication of 8p and 8q[28,29] and mutations in transcription factors NKX2.5[30] and Pitx2.[31] Evidence supporting rare autosomal recessive inheritance of truncus arteriosus in the absence of 22q11.2 deletion has been reported.[32]

## MORPHOLOGY

Truncus arteriosus is characterized by a single aortopulmonary trunk arising from the base of the heart, which gives rise to the coronary, systemic, and pulmonary arteries. An obligatory ventricular septal defect is present. The origin of the PAs varies considerably and forms the basis of the two major classification systems. Collett and Edwards[14] proposed the first widely accepted classification scheme in 1949. In their system, the spectrum of truncal variations is divided into four general categories based on the origin of the PAs. In type I truncus arteriosus, the left and right branch PAs arise from a single short main pulmonary trunk. The main pulmonary trunk commonly arises from the posterior aspect

of the truncus, just above the truncal valve. In type II truncus arteriosus, the origins of the left and right PAs are in close proximity to one another along the posterior aspect of the truncus. In type III truncus arteriosus, the origins of the left and right PAs arise more laterally and separate from one another. In type IV truncus arteriosus, the PAs arise from the descending aorta rather than the truncus (extrapericardial origin of the branch PAs). Although this configuration has historically been referred to as "pseudotruncus," it is now generally believed to represent a form of pulmonary atresia with aortopulmonary collateral vessels and should not be classified as a variation of truncus arteriosus.

An additional classification system was developed by Van Praagh and Van Praagh in 1965.[33] Like the Collett and Edwards classification systems, this system also divides truncus arteriosus into four categories. Type A1 is characterized by a main PA segment arising from the truncus due to a partially formed aorticopulmonary septum. Type A2 is characterized by the presence of left and right PAs arising independently from the truncus, irrespective of the proximity of their origins. Type A3 is characterized by the presence of a single PA arising from the truncus. In this form, often referred to as "hemitruncus," the contralateral lung is supplied by a pulmonary collateral vessel arising from either the distal aorta or the ductus arteriosus. Type A4 is characterized by a hypoplastic or IAA with PAs arising from a large ductus arteriosus. In this classification scheme the designation of type B indicates absence of a ventricular septal defect. However, because the presence of a true truncus arteriosus in these patients is questionable, the Van Praagh B classification is seldom used. These classification schemes share overlapping features and are schematically represented in Figure 72-1. Collett and Edwards type I and Van Praagh type A1 are essentially the same. Van Praagh type A2 encompasses the Collett and Edwards types II and III.

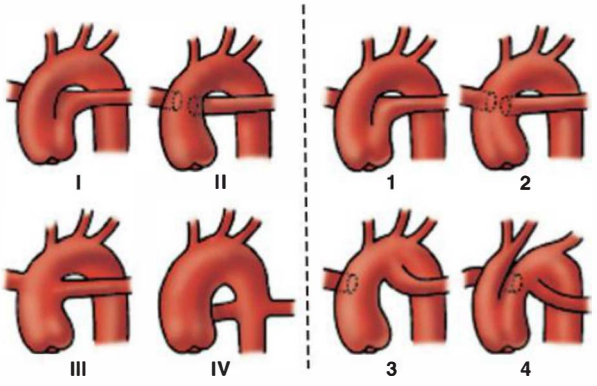



**FIGURE 72-1** Morphologic classifications of truncus arteriosus. The Collet–Edwards classification describes truncus types I to IV according to the origin of the branch pulmonary arteries, whereas Van Praagh's types 1 to 4 are subdivided according to presence (subtype A) or absence (subtype B) of associated ventricular septal defects (details in text). (From Vricella LA, Tsang VT. Truncus arteriosus. In: Yang SC, Cameron DE (eds). *Current Therapy in Thoracic and Cardiovascular Surgery*. Philadelphia: Mosby, 2004:751. With permission.)

In 2000, a new classification system was developed by the STS Congenital Heart Surgery Database Committee and representatives of the European Association for Cardiothoracic Surgery.[34] This system, based on the Van Praagh scheme, divides truncus arteriosus into three main categories: truncus arteriosus with confluent or near confluent PAs, truncus arteriosus with absence of one PA, and truncus arteriosus with IAA or coarctation. In this system, modifiers are used to denote the number of truncal valve leaflets, the presence and degree of truncal valve stenosis or insufficiency and the presence of ventricular hypoplasia, coronary artery anomaly, overriding truncal valve, transposition, or thymic aplasia. A similar nomenclature scheme to describe various methods of repairing or palliating truncus arteriosus has also been proposed. Although these classification systems may be very useful for risk-stratification analysis, the Van Praagh and Collett and Edward's classification systems continue to be widely used.

The truncal valve is most commonly tricuspid (about 50 percent), quadricuspid (about 30 percent), or bicuspid (about 5 percent). More than four cusps and, rarely, a single cusp may also be seen. Valve leaflets may be thickened and dysplastic, contributing to valvular insufficiency or stenosis. Despite these functional and morphologic variations, fibrous continuity between the truncal valve and the mitral valve is preserved. The tricuspid valve may be in fibrous continuity or may be separated from the truncal valve by a thin muscular band. The truncal valve typically overrides the interventricular septum and the subarterial ventricular septal defect in a balanced manner or may be more committed to the RV. Less frequently, the truncus arises predominantly from the left ventricle. The ventricular septal defect is normally located in the subarterial portion of the infundibular septum. The ventriculoinfundibular fold typically forms the posterior margin of the defect and separates it from the anterior leaflet of the tricuspid valve. Less commonly, the ventricular septal defect may extend posteriorly to the tricuspid valve annulus in the perimembranous outlet portion of the septum. The inferior margin of the ventricular septal defect is made up by the trabecula septomarginalis, and the superior margin typically extends to the truncal valve.

Coronary artery anatomy in truncus arteriosus may exhibit significant variability.[35] Two coronary ostia are generally present. The left coronary artery typically originates from the left portion of the truncus. It may originate high in the sinus of Valsalva or above the sinus in proximity to the takeoff of the PA. The right coronary artery typically originates from the right anterior portion of the truncus. However, an anterior descending coronary artery may originate from the right coronary artery and cross the RV near the infundibulum. In up to 18 percent of cases, a single coronary ostium originating from either the left or right is present. Additional coronary anomalies that have been reported include the circumflex artery originating from the right coronary artery, ostial stenosis due to structural deformation related to the

adjacent commissure, right coronary artery originating from the anterior descending coronary artery, and major coronary branches of the right coronary artery crossing the RV outflow tract to supply antero-basal surfaces of both ventricles and the upper portion of the interventricular septum.[36] Abnormal coronary anatomy must be carefully considered in planning surgical correction, because failure to recognize variations in coronary anatomy may cause or contribute to perioperative morbidity or mortality.[37]

Truncus arteriosus is generally associated with a left aortic arch, but a right aortic arch is present in approximately 30 percent of cases. Association with double aortic arch[38] and persistent embryonic fifth aortic arch[39,40] has also been reported. In approximately 15 percent of cases, the aortic arch is either interrupted or severely hypoplastic.[41] The interruption usually occurs distal to the origin of the left common carotid artery (type B aortic arch interruption; see Chapter 76) and is accompanied by ductal continuity with the descending thoracic aorta. In this morphologic variant, the PAs arise from the ductus arteriosus. Other associated abnormalities of the great vessels include IAA with postductal origin of all brachiocephalic vessels[42] and the absence of one PA.[43] Absence of one PA occurs most frequently on the same side as the aortic arch. Truncus arteriosus is also commonly associated with patent foramen ovale/secundum atrial septal defect and tricuspid insufficiency or stenosis.[44]

## PATHOPHYSIOLOGY

The physiologic features of truncus arteriosus are typical of those seen in other forms of cyanotic congenital heart disease with increased pulmonary blood flow. The single aortopulmonary trunk results in parallel pulmonary–systemic circulations, making intracardiac mixing of systemic and pulmonary blood at the level of the ventricular septum obligatory to maintain adequate systemic oxygenation. Additional mixing occurs at the level of the atrial septal defect when present (Fig. 72-2). During fetal development pulmonary blood flow represents less than 10 percent of the cardiac output due to increased pulmonary vascular resistance. At birth, the combined cardiac output traverses the truncal valve and the amount of pulmonary blood flow is determined by the change in pulmonary vascular resistance and the presence of any PA narrowing. Because the pulmonary vascular resistance initially falls below the systemic vascular resistance, severe hypoxia rarely occurs. When it does, proximal or distal PA narrowing must be suspected. As the pulmonary vascular resistance continues to fall during early postnatal life, pulmonary blood flow increases. Increased pulmonary venous return leads to volume overload of the RV, cardiopulmonary inefficiency, and congestive heart failure. Any degree of truncal valve incompetence can further increase the volume load on the ventricle, as well as compromise coronary perfusion due to diastolic flow reversal in the common trunk. The large, nonrestrictive ventricular septal defect enables pressure equilibration between the LV and RV, which leads to RV hypertrophy. Increased pulmonary blood flow, combined with systemic level arterial pressures within the pulmonary circulation, ultimately brings about pulmonary vascular changes that, in turn, increase pulmonary vascular resistance. Because the PAs originate above the truncal valve, the pulmonary circulation is exposed to systemic-level pressures during both systole and diastole. It is believed that this accelerates the abnormal pulmonary vascular changes leading to increased pulmonary vascular resistance and pulmonary hypertension. Although increased pulmonary vascular resistance and pressure generally occur several months later in life, there is evidence that early

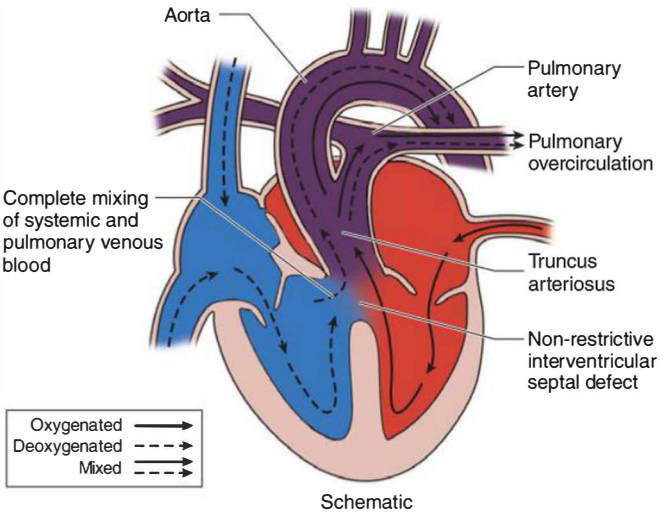



**FIGURE 72-2** Diagram illustrating the pathophysiology of truncus arteriosus. (From Reitz BA, Yuh DD (eds). *Congenital Cardiac Surgery*. New York: McGraw-Hill, 2002:153. With permission.)

molecular and cellular changes occur within a few weeks in the presence of increased pulmonary blood flow[45] and that observed vascular changes are related to alterations in nitric oxide and endothelin activity.[46] These findings may explain the improved outcomes associated with early surgical repair.

## CLINICAL FINDINGS

The clinical findings associated with truncus arteriosus depend on the degree of truncal valve competence, pulmonary vascular resistance, and coexisting cardiac defects. Shortly after birth, infants will generally exhibit mild cyanosis, tachycardia, tachypnea, costo-sternal retractions, and diaphoresis, which may worsen during feeding. The second heart sound is single and a harsh systolic ejection murmur may be audible at the left lower sternal border. A precordial thrill may be present. Pulmonary runoff produces a low diastolic pressure and widened pulse pressure. Truncal valve stenosis and insufficiency may produce a more pronounced ejection murmur or a diastolic decrescendo murmur, respectively. Cyanosis may improve as pulmonary vascular resistance continues to fall over the first few weeks. Increasing pulmonary overcirculation leads to progressive worsening symptoms of congestive heart failure, including pulmonary edema, hepatomegaly, and failure to thrive. These findings may develop at an accelerated rate or may be more pronounced in the setting of truncal valve insufficiency. Neonates not undergoing repair may exhibit improvement in heart failure symptoms but worsening of cyanosis as maladaptive pulmonary vascular changes progress and pulmonary blood flow decreases. Infants with Van Praagh type A4 truncus arteriosus (IAA, ductal origin of PAs) may exhibit symptoms of systemic hypoperfusion and ischemia as well as hypoxia as the ductus arteriosus begins to close shortly after birth. Features such as micrognathia, choanal atresia, and cleft palate may be found in patients with coexisting chromosome 22q11 deletion syndromes (Fig. 72-3).

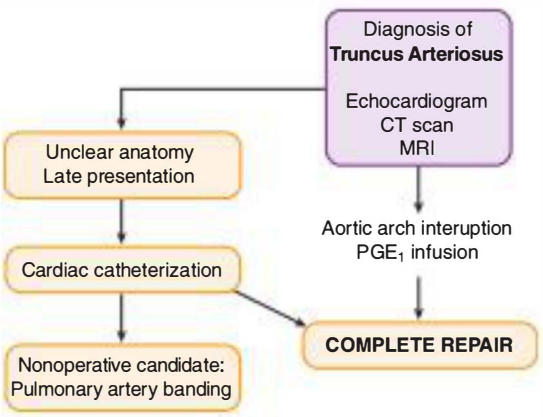



**FIGURE 72-3** Decision-making flowchart. Clinical decision-making algorithm for neonates with truncus arteriosus.

## Diagnostic Studies

Truncus arteriosus is most commonly diagnosed shortly after birth; however, prenatal diagnosis is becoming increasingly common as prenatal care becomes more accessible. All cyanotic infants should undergo careful diagnostic testing, including blood gas analysis, pulse oximetry, electrocardiography, chest radiography, and transthoracic or transesophageal echocardiography. Early pulse oximetric screening may detect evidence of truncus arteriosus before symptoms develop.[47] Biventricular hypertrophy is generally evident on the electrocardiogram and may become more pronounced over time. Although initial chest radiographs may appear normal, subsequent studies typically demonstrate cardiomegaly and increased pulmonary vascular markings. Absence of the thymic shadow may be observed in patients with coexisting neural crest disorders such as DiGeorge syndrome. A right-sided aortic arch may be apparent in approximately 30 percent of cases. Two-dimensional and Doppler echocardiography accurately detect truncus arteriosus and characterize important anatomic and hemodynamic features, including type of truncus, truncal valve morphology and function, presence of PA stenosis, size and location of the ventricular septal defect, location of coronary ostia, pulmonary blood flow and resistance, and presence of associated lesions.[48] Although the echocardiographic distinction between different conotruncal abnormalities is challenging in the fetus, truncus arteriosus may be accurately diagnosed by fetal echocardiography.[49] Accurate in utero diagnostic studies are invaluable in counseling parents. Cardiac catheterization and coronary angiography are useful for accurate anatomic and physiologic assessment of the PAs and to determine the precise orientation and course of the coronary arteries. This is especially important in older infants who may exhibit pulmonary vascular hypertrophic changes and in infants with echocardiographic evidence of coronary artery abnormalities. Computed tomography and resonance magnetic imaging with three-dimensional reconstruction are gaining wide acceptance as additional diagnostic tools.

## CLINICAL MANAGEMENT

The initial medical management of these patients should focus on the treatment of congestive heart failure and ensuring adequate oxygen delivery. Initial hypoxia may necessitate endotracheal intubation and mechanical ventilation. As pulmonary vascular resistance falls, decreased diastolic coronary perfusion may lead to worsening of heart failure symptoms, especially during feeding and crying. Diuretics, digoxin, and occasionally more powerful inotropic agents are useful in managing heart failure. Hypocalcemia must be corrected in patients with coexisting syndromes involving the deletion of chromosome 22q11. The findings of progressive tachycardia, hypotension, acidosis, and hypoxemia during early postnatal life suggest truncus arteriosus

with IAA (Van Praagh type A4). Intravenous prostaglandin therapy must be initiated to arrest closure of the ductus arteriosus. Genetic screening for chromosome 22q11 deletion should be undertaken in all patients with truncus arteriosus. Patients presenting later in life with evidence of advanced pulmonary vascular obstructive disease and pulmonary hypertension, may benefit from inhaled nitric oxide therapy. However, the prognosis for these children remains poor.

## Surgical Therapy

Initial surgical management of truncus arteriosus was limited to palliative PA banding, which resulted in survival rates similar to those observed in untreated patients. The first reported surgical repair utilizing a nonvalved Teflon conduit was performed in 1962.[6] Following this, McGoon and colleagues performed the first successful repair with a valved conduit in an older child in 1967.[7] Reports of successful repair and improved outcomes in younger infants[50] subsequently led to earlier repair and avoidance of maladaptive pulmonary vascular changes. Currently, banding of the PAs should be considered only when coexisting conditions such as sepsis, shock, or intracranial hemorrhage prevent surgical repair. Rarely, in cases where truncus arteriosus coexists with IAA, banding may be considered as initial palliation.[51]

The timing of surgical intervention in these patients has received considerable attention. Overall, the trend has been toward earlier repair in infants and neonates. Repair of truncus arteriosus during the first few weeks of life may be safely accomplished in the majority of patients[52] and appears to improve survival.[53] Early repair ameliorates congestive heart failure and failure to thrive and prevents irreversible pulmonary vascular disease. However, the overall operative mortality associated with neonatal correction of truncus arteriosus, estimated at 15.4 percent based on a recent large multi-institutional sample, remains relatively high compared with repair of other forms of complex congenital cardiac disease.[54–56] The reason for this discrepancy is unclear. A review of the strategy for management of truncus arteriosus by Brizard and colleagues[57] found that weight less than 3 kg is an independent risk factor for early perioperative mortality and that deferring surgery until 2 to 3 months of age decreases surgical risks. Although such a policy results in surgical intervention on infants of greater body weight and the use of larger valved conduits with associated longer freedom from reoperation, improved results may represent exclusion of neonates with otherwise unfavorable characteristics or risk factors. We prefer initial complete correction in infancy, except in unusual circumstances (extremely low-birth weight or prematurity, severe truncal valve dysfunction, arch anomalies), where we have used an initial palliative approach consisting of removal of the PAs from the truncus and subsequent connection to a 6-mm RV-to-PA (Sano-type) shunt. This procedure is then followed by complete intracardiac repair at a more favorable time.

## Operative Technique

We routinely employ intraoperative transesophageal echocardiography to evaluate valve function, intracardiac shunting, and wall motion before and after repair. Repair of a type 1 truncus arteriosus is depicted in Figure 72-4. Following median sternotomy, a generous portion of pericardium is harvested and treated with glutaraldehyde. The origin and course of the coronary arteries are carefully evaluated. The common arterial trunk, complete aortic arch, and great vessels are extensively mobilized. The PAs are mobilized well into the hilum and snares are placed. When a ductus arteriosus is present, care must be taken to avoid injuring it. In the presence of an IAA, snares are also placed around the great vessels. Arterial cannulation should be performed in the most distal ascending aorta or the transverse arch. Bicaval cannulae and a left ventricular vent are used to adequately decompress the heart. Snares are tightened to occlude the PAs upon initiation of cardiopulmonary bypass. If a ductus arteriosus is present, it is ligated. After distal aortic cross-clamping, cold blood cardioplegia is administered via an ascending aortic cannula and readministered intermittently throughout the procedure. In the setting of significant

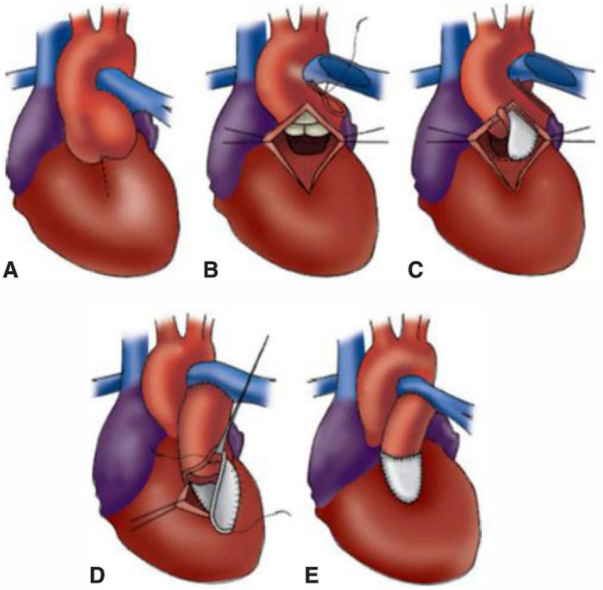



**FIGURE 72-4** Schematic rendition of complete repair of truncus arteriosus, Collet–Edwards, type I. The procedure entails septation of the truncus and a right ventriculotomy to perform ventricular septal defect (VSD) closure [dotted lines (**A**)]. Following septation of the truncus, the large VSD is exposed through a right ventriculotomy (**B**). The VSD is closed with a patch (**C**). Continuity between right ventricle and pulmonary arterial confluence is reestablished with a valved conduit and a proximal hood (**D**). Completed procedure (**E**). (From Vricella LA, Tsang VT. Truncus arteriosus. In: Yang SC, Cameron DE (eds). *Current Therapy in Thoracic and Cardiovascular Surgery*. Philadelphia: Mosby, 2004:753. With permission.)

truncal valve insufficiency, retrograde cardioplegia may be delivered via the coronary sinus. Alternatively, the common trunk may be opened just distal to the origin of the PAs and cardioplegia given directly into the coronary ostia. Topical iced slush is applied and the patient is cooled to 32°C.

In the presence of a clearly defined common PA, it is transected close to the common arterial trunk and the resultant truncal defect is closed with a Dacron patch and a running polypropylene suture. When the PAs arise separately, the common arterial trunk should be opened in a transverse fashion just distal to the origin of the PAs, which are divided proximally. This approach often enables primary closure of the aorta without distortion of the coronary ostia. When insufficiency is detected by echocardiography, complete transection of the common arterial trunk facilitates thorough evaluation of the truncal valve.

A longitudinal incision, originating at the base of the common arterial trunk, is performed in the anterior surface of the RV outflow tract. This incision must be modified if a significant coronary artery crosses this area.[36,37] The edges of the ventriculotomy are trimmed to create a smooth oval opening. When a sub-arterial ventricular septal defect is present, it is easily visualized and repaired though this incision. The septal defect is closed with a Dacron sauvage patch and either running or interrupted 6-0 polypropylene suture. Subarterial ventricular septal defects are commonly surrounded by a clearly defined circumferential rim of muscle. The superior aspect of the patch is sewn to the subvalvular aspect of the ventriculotomy by passing pledget-supported interrupted sutures through the anterior wall of the RV outflow tract. Injury to the conduction system is unlikely, as the system is separated from the septal defect by the posterior muscle tissue of the ventriculoinfundibular fold. In contrast, the conduction system is at risk in the setting of a perimembranous inlet type of ventricular septal defect, in which the defect extends to the tricuspid annulus. In this setting, we have found that approaching the defect through the right atrium provides the best exposure and facilitates suture placement through the base of the septal leaflet of the tricuspid valve. Sutures should be placed well away from the edge of posteroinferior margin of the defect so as to avoid injury to the conduction system. A patent foramen ovale or secundum atrial septal defect is typically present. Rather than completing closure of the defect, we prefer to leave in place some interatrial communication to allow right-to-left shunting in the early postoperative phase. This may be accomplished by partial closure or by closing the defect with a fenestrated autologous pericardial patch. The 2- to 4-mm fenestration may easily be closed at a later time using percutaneous techniques. With this approach, cardiac output can be safely maintained in the setting of postoperative pulmonary hypertensive crises.

A valved conduit is most commonly used to establish RV-to-PA continuity. Several types of conduit have been used successfully for this purpose, including aortic and pulmonary homografts,[58–61] composite bioprosthetic conduits,[62–64] pulmonary xenografts,[65,66] aortic xenografts,[67] autologous pericardial valved conduits,[68,69] and valved venous xenografts.[70–73] Choice of conduit is generally based on availability of homograft tissue and surgeon's experience and preference. Generally, pulmonary homograft tissue is preferred because it may offer improved valve longevity and is technically easier to sew than composite (Dacron) valved conduits.[59,74,75] Aortic homografts develop conduit stenosis at an accelerated rate in infants and children. The reported longevity of homograft conduits varies widely, with reported freedom from homograft replacement ranging from approximately 50 percent at 3 years[59] to approximately 75 percent at 10 years.[58] Aortic homografts develop conduit stenosis at an accelerated rate in infants and children compared to pulmonary homografts and other conduit types.[76] Conduit stenosis is the most common reason for reintervention (i.e., conduit replacement).[77] A recent prospective multi-institutional study by the Congenital Heart Surgeons' Society of conduit survival in children less than 2 years of age found that 40 percent will require a conduit-related intervention within 2 years of initial implant.[76] Multivariable risk factors for accelerated conduit failure included younger age at initial implant, presence of PA arborization abnormalities, and an initial conduit *Z*-score less than +1. Limited availability of small homografts is a significant limitation to the use of homograft conduits. Large adult homografts have been successfully downsized by longitudinal wall excision and conversion to bicuspid conduits.[78]

In general, composite xenograft conduits are more prone to calcification and early failure than homografts. Significant obstruction of the RV outflow tract occurs in up to 77 percent of patients within 12 months of surgery.[79] Actuarial freedom from reintervention following implantation ranges from 48 percent at 18 months[62] to 64 percent at 4 years,[80] depending on the type of conduit used. Small conduit size has also been identified as a risk factor for conduit failure in composite xenograft conduits.[80] Initial reports describing the use of stentless xenograft root conduits in these patients also describe limited conduit durability.[66,67]

The Contegra (Medtronic Inc., Minneapolis, MN) bovine jugular vein graft has more recently become popular for use as an RV-to-PA conduit. The graft is derived from a segment of bovine jugular vein that contains a naturally integrated tricuspid valve with associated sinuses. This graft offers several advantages, including superior tissue-handling characteristics, the availability of several sizes (12–22 mm), obviation of the need for proximal extension 'hoods' for infundibular shaping, and the ability to position the valve near the distal anastomosis. Data suggest that the Contegra conduit has improved durability compared to homografts especially in young children, though long-term data are lacking.[76,81] Widespread enthusiasm for the Contegra has been somewhat tempered by anecdotal reports of aneurysmal dilation,[82] thrombus formation,[83] and fibrotic membrane formation leading to distal conduit stenosis.[84]

Several methods have been devised to establish RV-to-PA continuity without the use of homografts or xenografts. Fresh autologous pericardial valved conduits have been

constructed and used in patients with truncus arteriosus.[69] Although preliminary follow-up indicates 66 percent freedom from reoperation at approximately 7 years, the mean age of these patients at initial operation was 6 months. Performed in younger patients, this technique has been associated with excellent freedom from reoperation but increased in-hospital mortality.[85] Direct RV-to-PA anastomosis has also been employed to reconstruct the RV outflow tract in patients with favorable PA anatomy.[86] Following direct posterior approximation, an anterior patch, with or without a pericardial monocusp, is fashioned from pericardium or Dacron. This repair is also associated with increased early mortality but improved freedom from reoperation at 8 to 10 years.[87,88] Although debatable, significant pulmonary insufficiency may be detrimental during the early postoperative period. The potential benefit of conduit growth must be weighed against pulmonary regurgitation in considering each of these repair techniques.

The distal conduit-to-PA anastomosis is completed first. In cases where the branch PAs arise from a single common pulmonary trunk, the common orifice may have to be enlarged to accommodate an appropriately sized conduit. This is especially true when a PA band has been placed previously. Enlargement of the PA orifice may be accomplished by incising the common pulmonary trunk laterally along the course of the one or both proximal branch PAs. The extent of lateral incision must be modified when there is a significant discrepancy in the size of the branch PAs. The incisions may have to be extended into the hilum in cases of severe branch stenosis or hypoplasia. The distal conduit is trimmed accordingly and anastomosed to the common pulmonary orifice using 6-0 polypropylene suture. In the setting of type I truncus with a relatively long common arterial segment, the pulmonary orifice may be sewn directly to the right ventriculotomy. Advantages of this method include capacity for growth and relative freedom from conduit stenosis.

The aortic cross clamp may be removed prior to construction of the proximal RV-to-conduit anastomosis. However, we find that the proximal anastomosis may be performed efficiently and most accurately on an arrested heart during a period of active rewarming. When an aortic homograft is used, it should be oriented so that the anterior leaflet of the mitral valve can be used as a hood to close the right ventriculotomy without distorting the homograft valve. Alternatively, a segment of Gore-Tex, bovine pericardium, Dacron, or homograft tissue may be used as an extension to close the remaining ventriculotomy. The valved portion of the homograft may be advanced toward the distal anastomosis to reduce the possibility of valve distortion caused by sternal compression. In this technique, the homograft is divided and the distal segment utilized for the proximal anastomosis. Irrespective of the technique used, narrowing of the ventriculotomy opening and distortion of the homograft valve must be avoided. After air has been carefully evacuated from the heart via an aortic root vent, the aortic cross clamp is removed. Once cardiac activity has been reestablished, the patient is weaned from cardiopulmonary bypass support. Transesophageal echocardiography provides important information regarding truncal and neopulmonic valve function and the presence of retained intracardiac air. Greater than mild truncal valve insufficiency should be addressed immediately by reinstituting full cardiopulmonary bypass, cooling, cardioplegic arrest, to achieve satisfactory valve repair. Consideration should be given to temporary left atrial and PA catheters. The additional hemodynamic information may be very helpful during the early postoperative period.

## Specific Technical Considerations

### DISCONTINUOUS PULMONARY ARTERIES

In cases where the left and right PAs arise from the common trunk in a noncontiguous manner, direct primary anastomosis of a common PA orifice to the right ventriculotomy is not possible. The left PA, which generally arises from the ductus arteriosus, is first mobilized and separated from ductal tissue at its origin. The right PA is then detached and the common trunk defect closed as described above. An aortic homograft is prepared for use as a conduit by removing the two proximal brachiocephalic vessels at their origin and ligating the left subclavian stump at its takeoff. The homograft is then anastomosed end to end to the shorter of the two PAs. The remaining PA is anastomosed end to side to the homograft at the site of the excised brachiocephalic vessels. The proximal anastomosis is performed as described above. Alternatively, a pulmonary homograft may be used if the branches are of sufficient length. A composite bioprosthetic conduit may be utilized in the absence of an appropriate homograft; however, the conduit's inherent stiffness may lead to distortion of the branch PAs.

### TRUNCUS ARTERIOSUS WITH INTERRUPTED AORTIC ARCH

Correction of truncus arteriosus with IAA is generally performed under hypothermic circulatory arrest. The ascending aorta, brachiocephalic vessels, and PAs are widely dissected to facilitate extensive mobilization of these structures. The origins of the first two to three intercostal arteries are divided to enable adequate mobilization of the descending aorta and permit a tension-free aortic reconstruction. We prefer to conduct cardiopulmonary bypass using bicaval and aortic/selective right subclavian artery cannulation. This approach provides excellent exposure for aortic reconstruction and permits low-flow antegrade cerebral perfusion during lower body circulatory arrest. The branch PAs are occluded with snares on initiation of cardiopulmonary bypass. A left ventricular vent is used to keep the heart adequately decompressed. The patient is cooled to 18°C and cerebral cooling packs are applied. Snares are used to occlude the innominate, left common carotid, and left subclavian arteries, and a clamp is used to occlude the descending aorta distal to the isthmus. Lower body circulatory arrest is accompanied by

low-flow antegrade cerebral perfusion. Care must be taken to avoid injury to the coronary arteries in separating the proximal main PA from the aorta. After carefully inspecting the truncal valve through this defect, the latter is closed using a patch, as described above. When an anomalous right subclavian artery arises from the descending aorta, it may be simply divided and ligated. After all ductal tissue has been resected, the lateral aspect of the aorta is incised at the origin of the left common carotid artery and the descending aorta is anastomosed end to side using 6-0 polypropylene suture. After the cannula has been removed from the descending aorta and air from the aorta, the brachiocephalic snares are removed and rewarming is initiated. RV-to-PA continuity is established as described above and the patient is weaned from cardiopulmonary bypass.

Critical compression of the left mainstem bronchus may occur following repair of truncus arteriosus with interrupted aortic arch. This can be avoided by adequate mobilization of structures during surgical correction and high vascular anastomosis at the level of the origin of the left common carotid artery to prevent direct airway compression by the reconstructed aorta. Critical bronchial compression must be considered in the setting of postoperative air trapping in the left lung, pneumonia, or failure to wean from ventilator support. Radiographic confirmation of bronchial compression warrants immediate revision of the aortic reconstruction. A 10-mm Gore-Tex interposition graft placed distal to the left subclavian artery may be used to lengthen the aortic arch and relieve tension on the bronchus by the "Gothic" reconstructed aortic arch. Replacement of this segment with a larger Dacron interposition graft can be performed safely through a left thoracotomy later in life.

The combination of truncus arteriosus and IAA carries high early mortality, and results from early neonatal repair remain poor. The largest series of 50 neonates from the Congenital Heart Surgeons Society reported overall survival from admission of 44 percent at 6 months.[41] Suboptimal outcomes with complete early correction have led to alternative strategies including bilateral branch PA banding with concomitant aortic arch repair initially, followed by delayed intracardiac repair.[51] Primary transplantation had also been advocated in this complex group, especially in the presence of sever truncal valve dysfunction.[41]

### TRUNCAL VALVE DYSFUNCTION

Morphologic and functional dysfunction of the truncal valve must be carefully evaluated using preoperative and postoperative transesophageal echocardiography and direct inspection during surgical correction. Preoperative insufficiency or stenosis may be caused by structural valve abnormalities, altered ventricular loading conditions, abnormal flow characteristics related to systemic-to-pulmonary runoff, or a combination of the two. Therefore, the degree of dysfunction noted during preoperative echocardiography may not accurately predict truncal valve function following surgical partition of the truncus arteriosus and complete intracardiac repair. We believe that any truncal valve dysfunction should be addressed during the initial corrective procedure. Every effort should be made to repair a dysfunctional truncal valve rather than replace it. Some degree of truncal valve insufficiency is present in more than one-third of patients.[89,90] Using a methodical approach to valve insufficiency, numerous repair techniques have been successfully employed.[89–95] The surgeon should be familiar with several repair methods because of the variability of underlying structural defects (See Chapter 81). Prolapsing cusps may be resuspended from the annulus using a pledget-reinforced 6-0 polypropylene mattress suture through the adjacent commissure. Careful resection of thickened cusp edges may improve leaflet apposition. Cusp augmentation, using autologous pericardium, has also been used in the setting of scarred and retracted leaflets.[96] Insufficiency associated with four or more leaflets may improve following suture approximation of incomplete commissures in partially fused leaflets to create a functionally bicuspid or tricuspid valve. Alternatively, leaflet excision and reduction annuloplasty with or without coronary reimplantation may be required in the setting of annular enlargement. Irrespective of the technique utilized, the fundamental goal of repair is to correct truncal insufficiency without narrowing the valve orifice.

Truncal valve stenosis is less common.[53] Stenosis due to leaflet abnormalities may also be amenable to valvuloplastic techniques, such as commissurotomy and debulking of myxomatous zones of coaptation. Resection of a subvalvular fibromuscular membrane should be undertaken when it contributes to stenosis. However, stenosis due to a critically small annulus or continued regurgitation following valve repair generally necessitates valve replacement with an aortic valve homograft (Fig. 72-5).[96,97] The truncus is transected just distal to the origin of the PAs and a right ventriculotomy is created, extending from the free wall of the RV outflow tract to the annulus of the truncal valve. The truncal root and leaflets are excised and coronary ostia buttons preserved. The aortic homograft is then sewn into place using 6-0 polypropylene suture. The homograft should be oriented so that the anterior leaflet of its mitral valve is used to close the ventricular septal defect. Alternatively, the mitral leaflet may be removed and the defect closed with a Dacron patch. The site for attachment of each coronary button is carefully planned to ensure a tension-free, unobstructed anastomosis. Windows are cut into the homograft and the ostia are sewn into place using 8-0 polypropylene sutures. After completion of the distal aortic anastomosis with 6-0 polypropylene, a second homograft (aortic or pulmonic) is used to construct a RV-to-PA conduit as described above.

## POSTOPERATIVE MANAGEMENT

During the early postoperative period, the patient must be vigilantly observed for evidence of RV dysfunction. Pulmonary hypertensive crises may occur in these patients, especially if surgical repair is undertaken after the neonatal

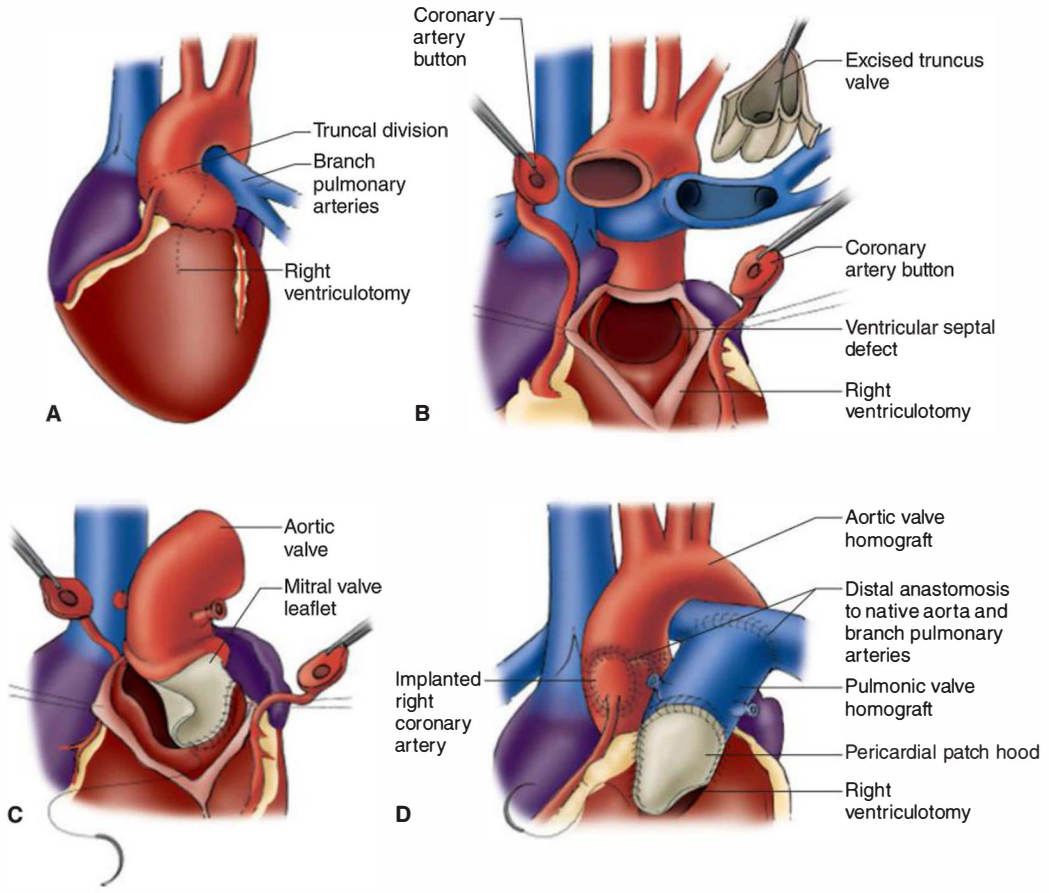



**FIGURE 72-5** Repair of truncus arteriosus, including truncal root replacement. The truncus is septated and the root excised (**A** and **B**). The VSD is closed with the anterior mitral valve leaflet attached to an aortic root homograft (**C**). The coronary buttons are reimplanted and a homograft is utilized to restore RV–PA continuity (**D**). (From Reitz BA, Yuh DD (eds). *Congenital Cardiac Surgery*. New York: McGraw-Hill, 2002:155. With permission.)

period. Early extubation and appropriate use of analgesic and anxiolytic agents are recommended to decrease the risk of pulmonary hypertensive episodes. A hemodynamically significant rise in PA pressure should prompt expeditious initiation of measures to reduce pulmonary vascular resistance, including increasing mechanical minute ventilation and fraction of inspired oxygen, administration of analgesics/anxiolytics, and inhaled nitric oxide. Echocardiographic evidence of acute truncal valve insufficiency, regional wall motion abnormalities, or RV-to-PA conduit obstruction or insufficiency warrant immediate surgical reintervention.

RV systolic and diastolic compliance may be poor because of prior exposure to systemic blood pressure. Accordingly, increased filling pressure may be required to optimize ventricular function. Important right-to-left shunting through the fenestrated atrial septum is not uncommon but generally decreases as RV compliance improves. Significant shunting may lead to cyanosis and suggests critical pulmonary hypertension. Postoperative dysrhythmia can contribute to significant myocardial dysfunction and decreased cardiac output. However, junctional ectopic tachycardia appears to occur less commonly following surgical intervention for truncus arteriosus than for other congenital cardiac anomalies.[98] Because truncus arteriosus is associated with an increased risk of developing necrotizing enterocolitis,[99] postoperative abdominal distention and feeding intolerance should be carefully evaluated.

## OUTCOMES

Outcomes for patients with truncus arteriosus have changed greatly since the introduction of surgical correction in the neonatal period. Increasing numbers of patients undergo nonpalliative, corrective surgery at an earlier age.[76,77,100,101] The trend of improved short- and long-term survival appears to be strongly related to earlier surgical intervention.[53] Surgical repair during the early neonatal period may prevent the development of detrimental pulmonary vascular changes and reduce the risk of postoperative death.[102]

Factors associated with increased mortality in these patients include other coexisting cardiac anomalies,[51,103] truncal valve insufficiency prior to repair,[104] and truncal valve replacement.[105] Early postoperative mortality is approximately 4 to 7 percent at 30 days.[91,106,107] The recent trend toward earlier surgical intervention complicates accurate determination of current long-term survival data; however, recent series have reported long-term survival rates up to 92 percent at 1 year,[106] 90 percent at 5 years,[105] 71 to 85 percent at 10 years,[105,108,109] 83 percent at 15 years,[105] and 60 percent at 20 years.[109] A significant number of late deaths may be related to reoperations.[105,107] The status of the truncal valve is an important predictor of subsequent reoperation. Approximately two-thirds of patients require truncal valve replacement within 10 years if truncal insufficiency is present at initial repair, whereas up to 95 percent of patients without truncal insufficiency at time repair do not require truncal valve replacement at 10 years.[105] Freedom from RV–PA conduit replacement varies according to several factors, including conduit size, type, PA architecture, and age at operation.[76] Cumulative freedom from conduit failure has been reported as approximately 80 percent at 1 year,[107] 50 percent at 10 years,[108,109] and 33 percent at 15 years.[109] Both surgical and nonsurgical methods may be employed to address the recurring problem of conduit failure in these patients. Conduit stenosis has been successfully managed using a percutaneous self-expanding stent.[76,110] The introduction of percutaneous pulmonary valve implantation will likely become another viable alternative to surgical intervention for conduit failure. Such nonsurgical methods may improve long-term outcomes by postponing higher-risk surgical interventions, or allowing implantation of larger conduits or in situ pulmonary valves. Trends toward improved short- and long-term survival indicate that increasing numbers of these patients will be cared for by members of the emerging field of adult congenital cardiac surgery.[111]

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## TRUNCUS ARTERIOSUS BOARD REVIEW QUESTIONS (CHAPTER 72)

1. Which genetic factor is not associated with truncus arteriosus?
   A. Transcription factor NKX2.5
   B. Chromosome 22q11 deletion
   C. Inactivation of GATA-6
   D. Microdeletion of chromosome 15q
   E. Duplication of chromosome 8p

2. Which is correct regarding classification of truncus arteriosus according to the Collett and Edwards system?
   A. Left- and right-branch PAs from single, short pulmonary trunk = type II
   B. Origins of left- and right PAs along posterior aspect = type III
   C. Origins of left- and right PAs more lateral and separate = type IC
   D. PAs arise from descending aorta = type IV
   E. "Pseudotruncus" = type III

3. Which is correct regarding coronary artery anatomy in truncus arteriosus?
   A. In up to 50 percent of cases, a single coronary artery is present.
   B. The left coronary artery typically originates from the left portion of the truncus.
   C. The right coronary artery typically originates from the right posterior portion of the truncus.
   D. The anterior descending coronary artery can arise from the right coronary artery.
   E. Three coronary ostia are usually present.

4. Which is correct regarding surgical technique for repair of truncus arteriosus?
   A. A composite bioprosthesis is the preferred conduit for discontinuous PAs.
   B. An anomalous right subclavian artery from the descending thoracic aorta can be ligated and divided in the setting of interrupted aortic arch.
   C. Compression of the left mainstem bronchus can be avoided by limiting the amount of mobilization and perform a low vascular anastomosis.
   D. The fundamental goal of repair is to correct truncal insufficiency by narrowing the common valve orifice.
   E. Postrepair stenosis is best treated by balloon valvuloplasty.

5. Which is true regarding outcomes after surgery for truncus arteriosus?
   A. Early mortality is 10 to 15 percent.
   B. Truncal valve stenosis prior to repair is associated with increased mortality.
   C. Long-term survival is 60 percent at 20 years.
   D. Late deaths are not related to reoperation.
   E. About 50 percent of patients without truncal insufficiency at initial repair will require truncal valve replacement at 10 years.

## ANSWERS

1. **Answer: D.** Microdeletion of chromosome 15q is not associated with truncus arteriosus. Mutations in transcription factor NKX2.5, 22q11 deletion, inactivation of GATA-6 within neural crest cell-derived smooth muscle cells, and duplications of chromosomes 8p and 8q have all been associated with truncus arteriosus.
2. **Answer: D.** Type IV is the classification when the PAs arise from the descending thoracic aorta. When the left- and right branch PAs from single, short pulmonary trunk, this is known as type I. Type II occurs when the origins of the left and right PAs is along the posterior aspect of the ascending aorta. Type III occurs when the origins of the PAs arise more laterally and separate from one another. "Pseudotruncus" was another historical term for type IV truncus arteriosus.
3. **Answer: B.** The left coronary artery typically originates from the left portion of the truncus, and the right coronary artery typically originates from the right anterior portion of the truncus. In nearly 20 percent of cases, there is a single coronary ostium; three coronary ostia are unusual. The right coronary artery can arise from the anterior descending artery.
4. **Answer: B.** In the setting of truncus arteriosus and IAA, an anomalous right subclavian artery from the descending thoracic aorta can be ligated and divided. Either a homograft or composite bioprosthesis can be used for discontinuous PAs; the composite graft, however, may lead to distortion due to inherent stiffness. Compression of the left mainstem bronchus is avoided by adequate mobilization and a high anastomosis. The fundamental goal of repair is to avoid narrowing the valve orifice. Postrepair stenosis generally requires valve replacement with a homograft.
5. **Answer: C.** Long-term survival is 60 percent at 20 years. Early mortality is approximately 4 to 7 percent. Truncal valve insufficiency prior to repair is associated with increased mortality. A significant number of late deaths can be attributed to reoperation. Up to 95 percent of patients without truncal insufficiency at initial repair will be free from truncal valve replacement.

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# Total Anomalous Pulmonary Venous Connection

*Ergin Kocyildirim*
*Victor O. Morell*

**KEY CONCEPTS**

- Epidemiology
  - Total anomalous pulmonary venous connection (TAPVC) accounts for 1 to 3 percent of all cases of congenital heart defects. Obstructed TAPVC is one of the few true emergencies in neonatal surgery.
  - TAPVC is either an isolated lesion or associated with complex atrial isomerism.
- Morphology
  - All the pulmonary veins drain into one or several systemic veins instead of the left atrium (LA).
  - The presence of an inter-atrial communication is crucial to sustain life and an atrial septal defect (ASD) or a patent foramen ovale (PFO) is considered as a part of TAPVC complex.
  - Four anatomic subtypes of TAPVC are recognized based on the location of the anomalous pulmonary venous drainage: supracardiac (40–50 percent), cardiac (20–25 percent), infracardiac (10–15 percent), and miscellaneous or mixed (10 percent).
- Pathophysiology
  - TAPVC is a mixing lesion in which pulmonary venous blood completely mixes with systemic venous blood and returns to the right atrium through a systemic vein, with consequent left-to-right shunt.
  - In neonates and small infants with obstructed pulmonary venous return, pulmonary hypertension and pulmonary edema are always present.
- Clinical features
  - Infants with obstructed TAPVC present with cyanosis, respiratory distress soon after birth. Infants with unobstructed TAPVC present later than infants with obstruction.
- Diagnosis
  - Echocardiography is diagnostic. Angiography is not indicated. Magnetic resonance imaging (MRI) may be useful as a supplement to echocardiography.
- Treatment
  - Surgical repair involves creation of a connection between the pulmonary venous confluence and the LA. Stabilization with preoperative extracorporeal membrane oxygenation (ECMO) is an option for desperately ill neonates.
- Outcomes
  - The long-term outcome for patients with repaired TAPVC is very good, with an operative mortality of 10 percent. Pulmonary venous stenosis is a relatively uncommon complication but, when it occurs, the impact on prognosis is profound.

## INTRODUCTION

Total anomalous pulmonary venous connection (TAPVC) is a rare and heterogeneous anomaly that accounts for only 2 percent of congenital heart defects.[1] TAPVC is a condition in which all the pulmonary veins drain into one or several systemic veins instead of the left atrium (LA). Presence or absence of pulmonary venous obstruction is important for the immediate postnatal stability of newborns. Obstructed TAPVC is one of the few true emergencies in congenital heart surgery.

The first attempt at surgical repair was performed by Muller in 1951 by performing an anastomosis between the pulmonary vein and the LA.[2] In 1956 Lewis successfully corrected TAPVC by using hypothermia and inflow occlusion.[3]

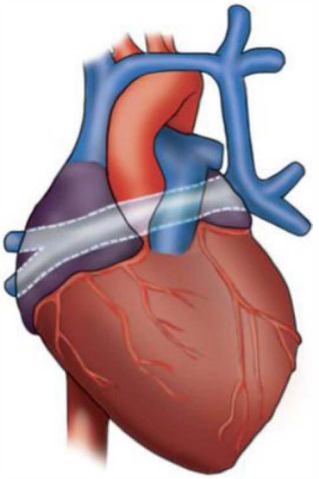


FIGURE 73-1 Supracardiac-type TAPVC. The vertical vein drains the pulmonary vein confluence into the innominate vein.

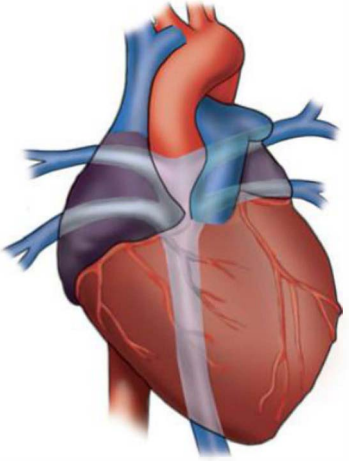


FIGURE 73-3 Infracardiac-type TAPVC. The descending vertical vein drains into the portal vein.

The first successful repair with cardiopulmonary bypass was performed by Burroughs and Kirklin in 1956.[4]

## ANATOMIC CLASSIFICATION

Four anatomic subtypes of TAPVC are recognized based on the location of the anomalous pulmonary venous drainage: supracardiac (40–50 percent), cardiac (20–25 percent), infracardiac (10–15 percent), and miscellaneous or mixed (10 percent). In supracardiac TAPVC, the four pulmonary veins join at a venous confluence (remnant of the common pulmonary vein) behind the LA and typically drain superiorly and to the left of the midline as the vertical vein (Fig. 73-1). This vertical vein will typically connect to the left innominate (brachiocephalic) vein. It may also connect directly with the superior vena cava (SVC) or, rarely, with one of the tributaries of the SVC. In the cardiac form of TAPVC, all four pulmonary veins drain into the common pulmonary vein, which in turn drains into the coronary sinus (Fig. 73-2). In infracardiac TAPVC, there is a common pulmonary vein behind the heart, which passes through the diaphragm and connects to either the portal vein, the ductus venous, or, rarely, directly to the inferior vena cava (IVC) (Fig. 73-3). Miscellaneous or mixed-type TAPVC is a combination of one or more of the other three types.

The etiology of TAPVC is unknown. TAPVC is most often an isolated lesion. Polysplenia, asplenia, and cat's eye syndrome can be seen associated with TAPVC. The presence of interatrial communication [atrial septal defect (ASD)] is necessary to sustain life. A patent foramen ovale (PFO) or patent ductus arteriosus (PDA) may also be present.

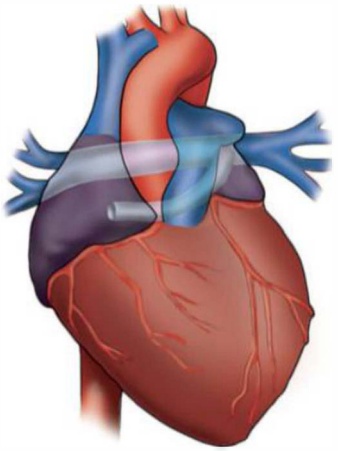


FIGURE 73-2 Cardiac-type TAPVC. The pulmonary vein confluence drains into the coronary sinus.

## PATHOPHYSIOLOGY

TAPVC is a mixing lesion in which pulmonary venous blood completely mixes with systemic venous blood and returns to the right atrium through a systemic vein with the presence of a left-to-right shunt. An unrestrictive right-to-left shunt (usually through an ASD or PFO) is necessary for left ventricular filling. Identical oxygen saturation in all chambers of the heart is very typical. Pulmonary venous obstruction is the most important determining factor for the severity of symptoms and emergency of the clinical presentation.

## CLINICAL FEATURES

Severe congestive heart failure is common in many patients in the early days of life, and is usually associated with cyanosis. Failure to thrive and slowly developing heart failure

can be seen within the first couple of months of life in the presence of unobstructed TAPVC. Infants with obstructed TAPVC are usually in critical condition.

## DIAGNOSTIC MODALITIES

Neonates with obstructed TAPVC will typically disclose normal heart size with gross pulmonary edema on chest x-ray. In neonates and small infants, the differential diagnosis should include surfactant deficiency, severe pneumonia and lymphangiectasia. Right ventricular hypertrophy is present on electrocardiogram (ECG). Prenatal echocardiography is suboptimal for the detection of TAPVC. Postnatal echocardiography will usually show large right-sided and small left-sided cardiac structures, and identify the anatomic subtype of TAPVC with accuracy. The features of supracardiac TAPVC can be defined by imaging left SVC flow. A large coronary sinus is usually present in the cardiac-type TAPVC. In the infradiaphragmatic-type TAPVC, the common pulmonary vein can usually be reliably defined as it courses through the diaphragm. Cardiac catheterization is no longer used in diagnosis. Although echocardiography is usually adequate for diagnosis, magnetic resonance imaging (MRI) with three-dimensional reconstruction may be valuable and used as a supplement (Fig. 73-4).

Infants with unobstructed TAPVC are not severely ill but will often have a history of failure to thrive and present with symptoms later than patients with obstructed TAPVC. Increased pulmonary flow can be seen on chest x-ray, and the so-called "snowman heart" with ground-glass appearance of the lung fields is a very characteristic sign.[5] Except for the presence of obstruction, echocardiographic findings are similar to the ones in obstructed TAPVC. Subdiaphragmatic drainage is a very unusual finding in infants with unobstructed TAPVC.

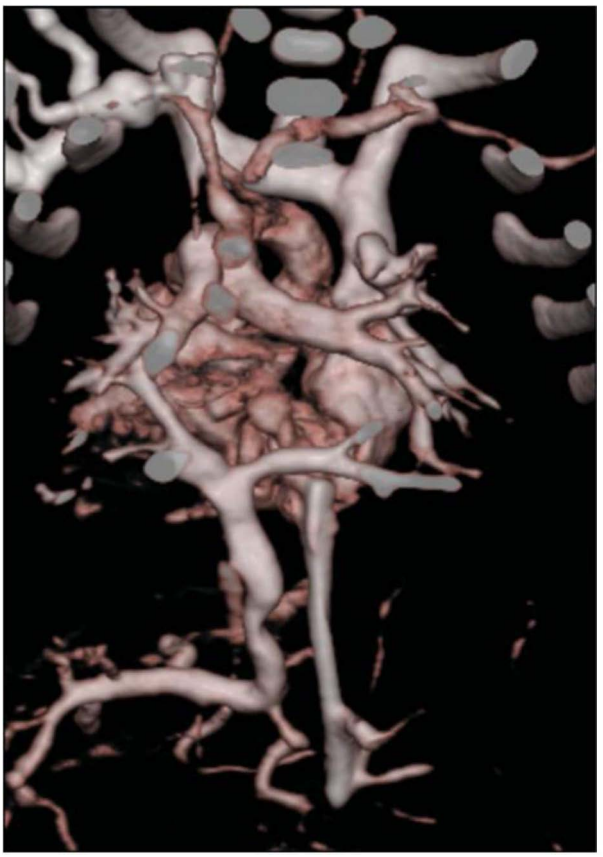


**FIGURE 73-4** Three-dimensional cardiac magnetic resonance imaging reconstruction in a neonate with mixed-type TAPVC (posterior view). On the right side, the upper and middle lobe pulmonary veins drain into the posterior aspect of the SVC. Both lower lobes drain along an infracardiac route. The left upper lobe vein is not well seen, but the vertical vein appears obstructed. (Image courtesy of Dr. Philip Spevak, Johns Hopkins Pediatric Cardiology)

## MEDICAL THERAPY

Preoperative medical therapy in the stable, unobstructed patient will usually consist of diuretic therapy. The management of severely ill infants with obstructed TAPVC can be, on the contrary, very challenging. The goal should be to quickly improve oxygenation and cardiac output, and to avert end-organ damage in anticipation of emergent TAPVC repair. Occasionally, due to intractable hypoxemia and acidosis, this is unachievable without resorting to preoperative extracorporeal membrane oxygenation (ECMO). Such infants are stabilized for 1 to 2 days and then taken to the operating room for repair.

## SURGICAL THERAPY

TAPVC requires surgical correction and remains, as mentioned above, one of the true surgical emergencies in neonatal cardiac surgery. The surgical management of patients with supracardiac and infracardiac TAPVC is similar. After identifying the anatomy precisely, repair requires an anastomosis between the pulmonary vein confluence and the LA. The ASD is routinely closed through a right or left atriotomy. It is our practice to always ligate the vertical or decompressing vein in order to prevent a postoperative left-to-right shunt at this level (Fig. 73-5).

Repair of TAPVC starts with the initiation of cardiopulmonary bypass. The PDA is routinely ligated. At 18 °C, cardiac arrest is provided with a single dose of antegrade cardioplegia and the patient's blood volume is drained into the reservoir. A period of profound hypothermic circulatory arrest (PHCA) is started. There are several advantages associated with PHCA: operating in an asanguinous field, the utilization of single venous cannulation, and the ability to retract the heart extensively with exposure of the retrocardiac structures. In a patient with levocardia, the heart is retracted

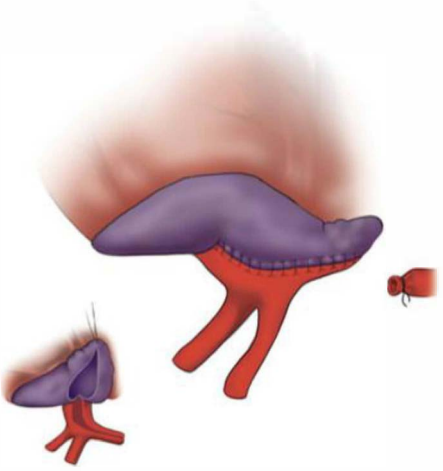


FIGURE 73-5 Supracardiac TAPVC repair with the apex of the heart elevated and retracted rightward, the left atrium and the pulmonary vein confluence are opened and the anastomosis is performed. The vertical vein is ligated and divided.

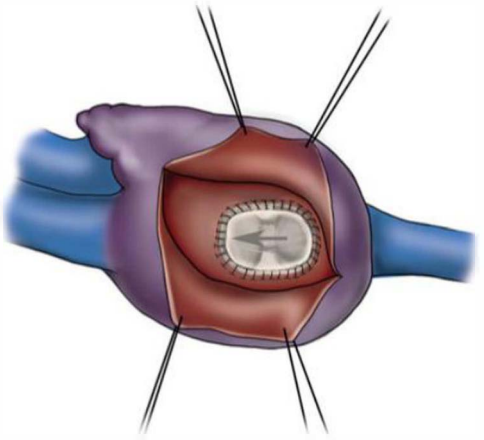


FIGURE 73-6 Cardiac TAPVC repair. **A.** Through a right atriotomy anatomy is visualized. **B.** The coronary sinus is unroofed into the left atrium. **C.** The coronary sinus and the atrial septal defect are closed with a single patch, effectively creating a new venous channel by which blood from the coronary sinus is routed into the left atrium.

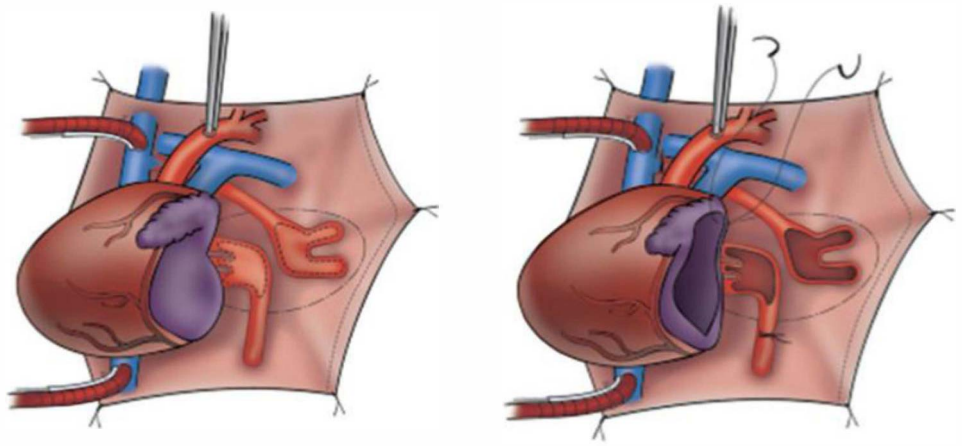
superiorly and to the right, and the pulmonary venous confluence is exposed. The typical retraction of the heart necessary to perform the anastomosis was first described by Williams et al. in 1964.[6] The pulmonary veins and their connections are posterior to the pericardium and can be occasionally difficult to dissect. As mentioned earlier, the ascending or descending vertical vein is then ligated. When the ascending vein drains to the left innominate vein, care should be taken to avoid left phrenic nerve injury. With the apex of the heart elevated and retracted rightward, corresponding incisions are performed and an anastomosis between the pulmonary venous confluence and the LA is performed in continuous fashion with a 7-0 polypropylene suture. If at all possible, the suture line should not involve the ostia of the pulmonary veins to avert the possibility of stenosis. The ASD is then closed by direct suture techniques or with a patch. Cardiopulmonary bypass is re-established and de-airing of the heart is performed before unclamping the aorta. Then the patient is rewarmed slowly. Weaning from cardiopulmonary bypass is undertaken at 36°C. The surgical repair is then checked by echocardiography, although some prefer to avoid transesophageal echocardiography (TEE) altogether in these patients because of the possibility of pulmonary venous compression by the rigid TEE probe. Hawkins described another commonly used technique that involves a right atrial approach with excision of the interatrial septum in order to access the LA.[7] This technique requires opening the posterior wall of the LA and performing the anastomosis to the common pulmonary venous confluence from within the atrium, as opposed to an extracardiac anastomosis such as the one described above. The interatrial septum is then closed with a patch, so as to effectively augment the size of the LA. Several modifications of this technique have also been reported.[8,9]

In the cardiac type TAPVC, the veins drain into the right atrium either directly or via the coronary sinus (Fig. 73-6). Cardiopulmonary bypass with bicaval cannulation and mild hypothermia to 34°C is initiated. After induction of cardioplegic cardiac arrest, the right atrium is opened. If the vein is draining into the right atrium directly, the repair consists of funnelling the pulmonary venous return into the LA through the ASD. The ASD usually needs enlargement, and a piece of pericardium is used to create the pulmonary venous channel. If the veins are draining via the coronary sinus, unroofing of the coronary sinus into the LA and patch augmentation of the pathway (effectively ASD Closure) are required. Extra care should be taken to avoid injury to the AV node.

The mixed-type TAPVC requires the combination of the previous two techniques and/or direct reimplantation in the LA appendage for left-sided lesions. On occasion, a single anomalous pulmonary vein can be left uncorrected without major hemodynamic consequence from a minor left-to-right shunt.

## RESULTS

The long-term outlook for TAPVC patients is very good, with an operative mortality of 10 percent and long-term survival rate approaching 85 percent.[10] Predictors of poor outcome are residual or de novo postoperative pulmonary venous obstruction and the presence of associated cardiac anomalies.[11–13] Recurrent pulmonary venous obstruction typically develops in the first few months after the repair, but could also present later. This postoperative complication is seen more frequently in the infradiaphragmatic and mixed types. Both Lacour-Gayet et al. and Najm et al. described a



A B

**FIGURE 73-7** Primary "sutureless" technique for repair of difficult or mixed venous drainage patterns in TAPVC. The heart is retracted and the pulmonary veins are exposed (mixed type, **A**). The pulmonary veins are incised and the pericardium surrounding them is sutured to the edges of the left atriotomy (**B**).

"sutureless" technique with in situ pericardium for relief of postoperative pulmonary venous stenosis.[14,15] This ingenious technique involves creation of a baffle with autologous pericardium. The veins are opened and allowed to drain into a pouch that funnels the blood into the LA (Fig. 73-7).[16] This technique can also be used as a primary form of drainage for small veins and the mixed type, in which a direct anastomosis between LA and veins would be difficult.

A simple excision of pulmonary venous obstruction after the repair of TAPVC has also been described by other surgeons.[17] For patients who survive surgery and do not develop early recurrent pulmonary venous obstruction, the long-term outlook is fair.[10]

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## TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION BOARD REVIEW QUESTIONS (CHAPTER 73)

1. Which is true regarding anatomic classification of total anomalous pulmonary venous connection (TAPVC)?
   A. Supracardiac form occurs in 10 to 15 percent.
   B. Cardiac form occurs in 40 to 50 percent.
   C. Infracardiac form occurs in 20 to 25 percent.
   D. Mixed form occurs in 10 percent.
   E. An interatrial septal defect is not necessary to sustain life.

2. Which is correct regarding clinical presentation and diagnosis of TAPVC?
   A. Severe congestive heart failure is common and is not associated with cyanosis.
   B. If the TAPVC is unobstructed, presentation may be delayed.
   C. A large coronary sinus is usually present in the supracardiac form.
   D. Subdiaphragmatic drainage is a common finding in unobstructed TAPVC.
   E. Echocardiography typically shows small right-sided structures and large left-sided structures.

3. Which is correct regarding surgical repair of TAPVC?
   A. The Hawkins technique involves a right atrial approach.
   B. Unroofing of the coronary sinus into the right atrium is required if the TAPVC drains into the coronary sinus.
   C. The ductus arteriosus is routinely incorporated into the repair.
   D. The vertical vein is left patent in order to decompress the heart.
   E. Hypothermic circulatory arrest is necessary for repair of the cardiac form.

4. Which is correct regarding outcomes after surgery for TAPVC?
   A. Operative mortality is less than 5 percent.
   B. Associated cardiac anomalies are not a risk factor.
   C. Recurrent pulmonary venous obstruction typically develops after the first few months after repair.
   D. Recurrent pulmonary venous obstruction is seen more frequently in the supracardiac form.
   E. The sutureless technique can be used as a primary repair in the mixed form.

## ANSWERS

1. **Answer: D.** The mixed form occurs in 10 percent. The supracardiac form occurs in 40 to 50 percent, the cardiac form occurs in 20 to 25 percent, and the infracardiac form occurs in 20 to 25 percent. An interatrial septal defect is required to sustain life.
2. **Answer: B.** If the TAPVC is unobstructed, the presentation may be delayed for the first few months of life. Severe congestive heart failure with cyanosis is the usual presentation. A large coronary sinus is usually present in the cardiac form. Subdiaphragmatic drainage is very unusual if the TAPVC is unobstructed. Echocardiography typically shows large right-sided- and small left-sided structures.
3. **Answer: A.** The Hawkins technique uses a right atrial approach to access the LA after excising the interatrial septum. If the TAPVC drains into the coronary sinus, this is unroofed into the left atrium. The ductus arteriosus and vertical veins are usually ligated to prevent postoperative left-to-right shunting. Hypothermic circulatory arrest is not required to repair the cardiac form of TAPVC.
4. **Answer: E.** The sutureless technique is useful in patients with small veins and the mixed form. Operative mortality is about 10 percent, and associated cardiac anomalies are a risk factor. Recurrent pulmonary venous obstruction typically develops within the first few months after repair and is seen more frequently in the infracardiac and mixed forms.

74

# Transposition of the Great Arteries

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## KEY CONCEPTS

- Epidemiology
  - Transposition of the great arteries (TGA) is the most common cyanotic cardiac anomaly, accounting for approximately 10 percent of congenital cardiac malformations.
- Morphology
  - The aorta arises from the right ventricle (RV) and the pulmonary artery (PA) from the left ventricle (LV). More than 50 percent of patients have an intact ventricular septum (IVS), while the remainder is split between a ventricular septal defect (VSD) with and without pulmonary stenosis (PS). The coronary artery pattern is variable; the most common one involves the left circumflex and left anterior descending (LAD) coronary arteries arising from the leftward and the right coronary artery (RCA) from the rightward sinus, respectively.
- Pathophysiology
  - Systemic and pulmonary circuits are in parallel, with the degree of cyanosis depending on mixing at the atrial septal defect (ASD), patent ductus arteriosus (PDA), or VSD level, as well as with the degree of coexisting PS.
- Clinical features
  - In the absence of PS, pulmonary overcirculation ensues, with variable cyanosis determined by the adequacy of mixing. Cases of TGA with adequate PS and VSD can remain asymptomatic for a prolonged period. Infants with late presentation exhibit LV deconditioning from prolonged exposure of the LV to low pulmonary pressures.
- Diagnosis
  - Electrocardiography (ECG) and chest x-ray (CXR) suggest the diagnosis in the cyanotic newborn. Echocardiography defines the relationship between the great vessels, associated ASD/VSD/PDA/coronary patterns and estimates LV pressures. Cardiac catheterization is rarely required in the current era.
- Treatment
  - In patients with an IVS, severe cyanosis can be improved with percutaneous intervention (balloon or blade atrial septostomy). The arterial switch operation (ASO) with or without VSD closure is the operation of choice, performed after LV training with PA banding in patients with a deconditioned LV. In patients with significant PS and cyanosis, temporary palliation with a modified Blalock–Taussig shunt can be performed before repair with a Rastelli or Nikaidoh operation.
- Outcomes
  - Excellent outcomes are reported, with an operative mortality of less than 5 percent; long-term complications are represented by supravalvar PS, neoaortic regurgitation or stenosis, and coronary insufficiency.

## INTRODUCTION AND MORPHOLOGY

Transposition of the great arteries (TGA) is a common congenital cardiovascular malformation characterized by ventriculoarterial discordance. This discordant anatomy is defined by the fact that the aorta arises from the morphologic right ventricle (RV) and the pulmonary artery (PA) from the morphologic left ventricle (LV). The anatomy of TGA is best understood in the context of Van Praagh's segmental anatomy, a three-letter nomenclature system in which the atria, the cardiac looping, and the position of the great vessels are used to describe cardiac malformations (see Chapter 59). The first letter (S, I, or A) describes atrial *situs* (*solitus, inversus, or ambiguus*). The second letter (D or L) refers to the *dextro* or *levo* looping of the primitive cardiac tube during fetal development, which determines in turn whether atria and ventricles are concordant [D-looping, right atrium (RA) attaches to RV and left atrium (LA) attaches to LV] or discordant. The third letter describes the relative position of the great vessels. The letter S signifies normally related great vessels, and I denotes normally related but inverted great vessels. D or L describes the rightward or leftward position of the aorta relative to the PA in the setting of transposition. Hence in a normal heart, there is atrial *situs solitus*, *dextro* looping, and normally related great vessels, or (S, D, S).

In general, TGA is subclassified in *dextro* (or D-TGA) and *levo* (or L-TGA) transposition, referring to the position of the aorta relative to the PA (the last letter of the segmental anatomy classification scheme described above). In TGA, there is generally *situs solitus* of the atria. D-TGA is invariably associated with D-looping, resulting in a segmental anatomy of (S, D, D). L-TGA is characterized by atrioventricular and ventriculoarterial discordance (RA attaches to LV and LA to RV), and is alternatively termed *congenitally corrected TGA*. This association of L-looping with L-TGA results in an anatomy coded as (S, L, L). Other extremely rare forms of TGA, including (S, D, L), have been described but are beyond the scope of this chapter. However, the treatment options are generally similar. From a strictly morphologic standpoint, there should only be two forms of transposition: D-TGA, properly termed *transposition of the great arteries,* and L-TGA, which should be referred to as *congenitally corrected transposition.*

These are distinct clinical entities, each with several subtypes requiring a number of diverse reconstructive approaches; they are dealt with in separate sections of this textbook. With all forms of D-TGA, there is the need to maintain adequate mixing of oxygenated and deoxygenated blood between the right and left sides of the heart. The circulation in D-TGA is one of two separate circuits, pulmonary and systemic, in parallel (Fig. 74-1). Without communication between the two sides of the heart, deoxygenated blood does not reach the lungs and oxygenated blood does not reach the systemic circulation.

Although TGA was first described by Baillie in 1797,[1] the term *transposition* is credited to Farre, who used "transposition of the aorta and PA" to describe the malformation in 1814.[2] The term was further refined by Van Praagh[3] in 1971 to define *transposition* as ventriculoarterial discordance; the term *malposition* was reserved to positional anomalies of the great arteries observed in other lesions.

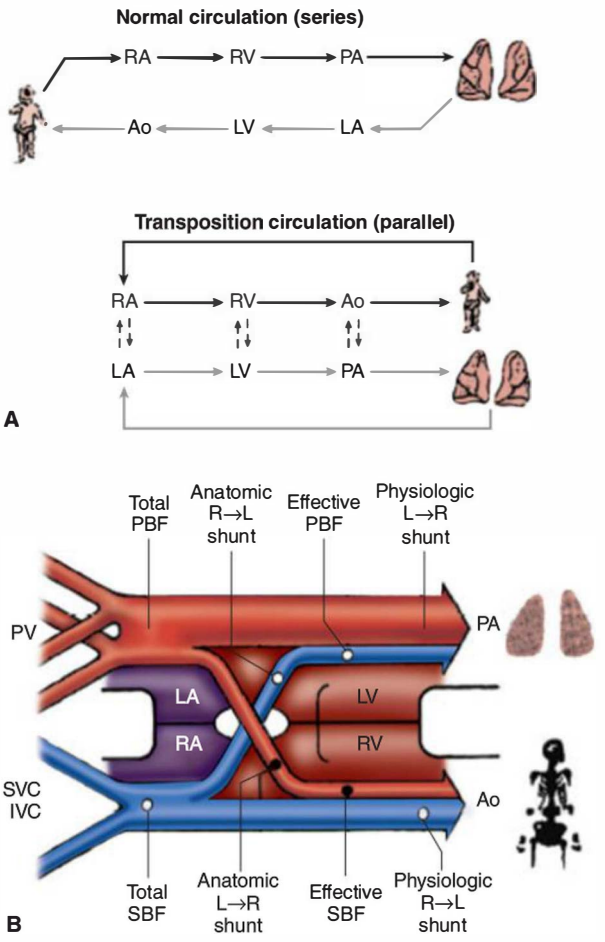



**FIGURE 74-1** Pathophysiology of D-transposition of great arteries (D-TGA). **A.** Systemic and pulmonary circuits in series with normally related great vessels and in parallel with D-TGA. **B.** Flows and shunts in D-TGA with intact ventricular septum. Solid arrows, deoxygenated blood; stippled arrows, oxygenated blood; dashed arrows, intercirculatory shunts; Ao, aorta; IVC, inferior vena cava; L, left; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PBF, pulmonary blood flow; PV, pulmonary veins; R, right; RA, right atrium; RV, right ventricle; SBF, systemic blood flow; SVC, superior vena cava. (From Wernovsky G. Transposition of the great arteries. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ (eds). *Moss and Adams' Heart Disease in Infants, Children and Adolescents,* 6th ed. Philadelphia: Lippincott, Williams & Wilkins, 2001:1038. With permission.)

Initial surgical therapies for TGA were palliative, aimed at increasing intracardiac mixing and improving systemic oxygen saturation. In 1950, Blalock and Hanlon described a technique for performing an atrial septectomy without cardiopulmonary bypass (CPB) to improve mixing at the atrial level.[4] Edwards, Bargeron, and Lyons later reported a modification of the Blalock-Hanlon atrial septectomy in which

the atrial septum was repositioned posterior to the right pulmonary veins, baffling them to the RA.[5] Other partial atrial-level switch procedures were devised by Lillihei and Varco,[6] who anastomosed the right pulmonary veins to the RA and the inferior vena cava (IVC) to the LA, and by Baffes, who performed a similar procedure with an allograft conduit from the IVC to LA.[7]

The first attempts at anatomic correction were directed at switching the two great vessels. Throughout the 1950s, a number of techniques for arterial-level switch operations were described, some including the transfer of one or both coronaries, but most leaving them in the pulmonary circuit. Although they were universally unsuccessful, these pioneering procedures laid the groundwork for the understanding of critical concepts for future procedures, including coronary anatomy and the importance of an LV prepared to handle system workloads. The first successful repairs were once again directed at the atrial level. In 1959, Senning accomplished the first successful atrial-level switch with a series of complex intraatrial baffles of native atrial tissue.[8] This technique was simplified in 1963 by Mustard with the use of prosthetic material.[9] The "Mustard procedure" became quickly the treatment of choice for D-TGA and remained such until Jatene reported the first successful arterial switch operation (ASO) in 1975.[10] Jatene and other authors demonstrated the long-term benefits of a true anatomic repair, which could be achieved with acceptable operative mortality. Although the Mustard and Senning operations are no longer used as primary therapy for D-TGA, they remain important for the treatment of L-TGA, which is discussed in greater detail in Chapter 75.

Several theories have been put forth regarding the embryology of D-TGA. Some authors support the theory that the normal spiral septation of the conotruncus does not occur, and that development of a straight septum results in transposition.[11–13] Van Praagh and Van Praagh have postulated that the etiology is persistence of the subaortic conus and reabsorption of the subpulmonary conus, leading to pulmonary-mitral continuity and, ultimately, TGA.[14] Other theories also propose a similar abnormal development of pulmonary-mitral continuity or of the area below the semilunar valves, or an abnormality of hemodynamics and blood flow as the etiology.[15]

D-TGA can be subdivided into D-TGA with intact ventricular septum (IVS) (55–60 percent), and D-TGA with ventricular septal defect (VSD) (40–45 percent). In D-TGA/VSD, one-third of the ventricular defects are hemodynamically insignificant. The VSDs are most commonly of the perimembranous or outlet morphologic types. Pulmonic stenosis (PS), causing significant left ventricular outflow tract obstruction (LVOTO), occurs rarely with an IVS. It is not uncommon to measure a preoperative gradient across the left ventricular outflow tract (LVOT) due to shifting of the septum from the high-pressure RV outflow tract (RVOT) to the lower-pressure LVOT in D-TGA/IVS. However, the gradient will resolve with anatomic correction and shift of the septum rightward. Hemodynamically significant PS occurs in approximately 10 percent of D-TGA/VSD and may affect operative decision making.[16]

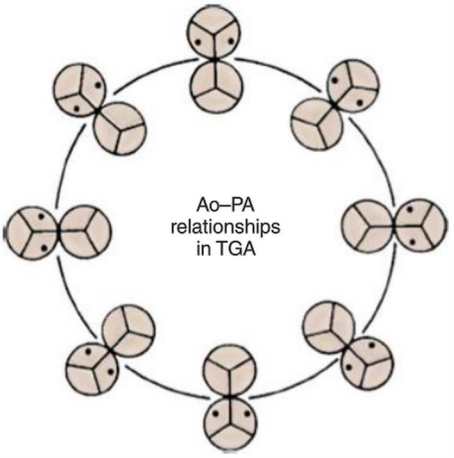



**FIGURE 74-2** The range of the relative positions of the aorta and PA in transposition of the great arteries. AO, aorta; PA, pulmonary artery; TGA, transposition of the great arteries. (From Mavroudis C, Backer CL. Transposition of the great arteries. In: Mavroudis C, Backer CL (eds). *Pediatric Cardiac Surgery,* 3rd ed. Philadelphia: Mosby, 2003:442. With permission.)

The relative positions of the aorta and PA are variable in TGA (Fig. 74-2). Fortunately, the sinuses of Valsalva of the aorta and PA tend to be arranged in a mirror-image alignment. This arrangement facilitates coronary transfer during the ASO. Similarly, the coronary artery arrangement can be variable. In the current era, most of these coronary artery patterns do not represent an obstacle to surgical correction (as discussed below). To standardize the definition of the coronary anatomy, the sinuses are conventionally numbered 1 and 2. If one imagines oneself standing in the nonfacing aortic sinus looking at the pulmonary root (Fig. 74-3),

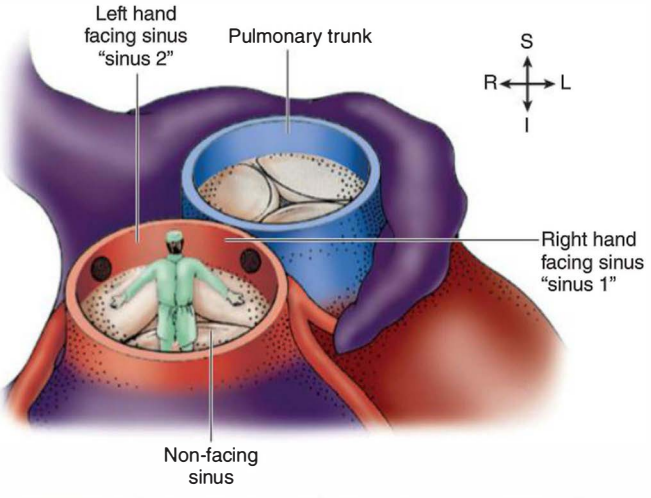



**FIGURE 74-3** Conventional numbering (Leiden convention) of the aortic sinuses for defining the coronary patterns. The illustration shows the typical coronary arrangement in D-TGA. (From Lesions in abnormally connected hearts. In: Wilcox BR, Andreson RH (eds). *Surgical Anatomy of the Heart,* 2nd ed. London: Gower, 1992. With permission.)

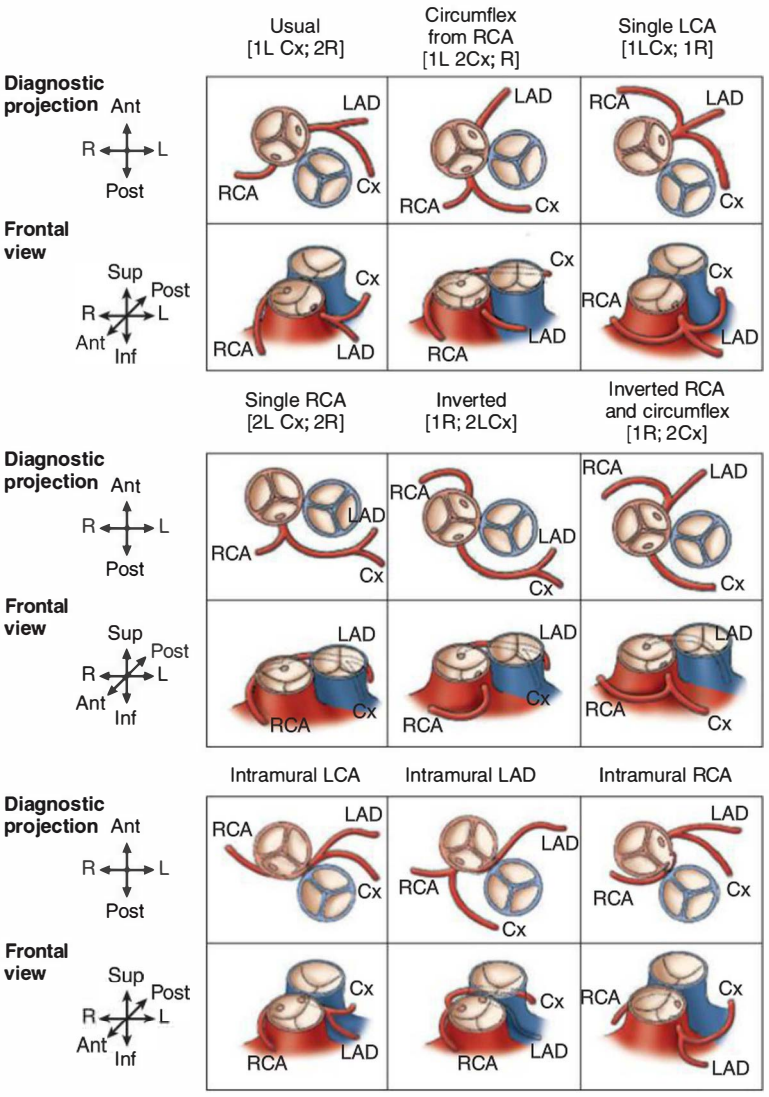



**FIGURE 74-4** Coronary artery patterns in TGA. Upper panel: Two-dimensional echocardiographic view. Lower panel: "surgeon's view." Ant, anterior; Cx, circumflex; Inf, inferior; L, left; R, right; LAD, left anterior descending; Post, posterior; RCA, right coronary artery; Sup, superior. (Modified from Wernovsky G, Sanders SP. Coronary artery anatomy and transposition of the great arteries. *Coron Artery Dis* 1993;4(2):148–157.)

the right-hand sinus is numbered as 1 and the left-hand sinus as 2. Using this convention (also known as the "Leiden" convention), the coronary anatomy is then described based on the sinuses of origin of the various coronary artery branches. For example, in the most common arrangement, the left anterior descending and circumflex coronary arteries arise from sinus 1 and the right coronary artery (RCA) from sinus 2. This pattern, as seen in Figure 74-3, is described as 1LCx2R. The common coronary arrangements are summarized in Figures 74-4 and 74-5.

## PATHOPHYSIOLOGY

As mentioned above, the circulation in D-TGA consists of two circuits in parallel (Fig. 74-1A). Deoxygenated blood is ejected to the body from the RV into the aorta, returning via the venae cavae to the RA and back to the RV. The oxygenated blood cycles from the LV to the PA and through the lungs to return once again to the LA and LV. Thus, intercirculatory shunting is required for mixing to occur. As reflected in Figure 74-1B, the *effective* pulmonary blood flow (the amount of deoxygenated blood reaching the lungs) is

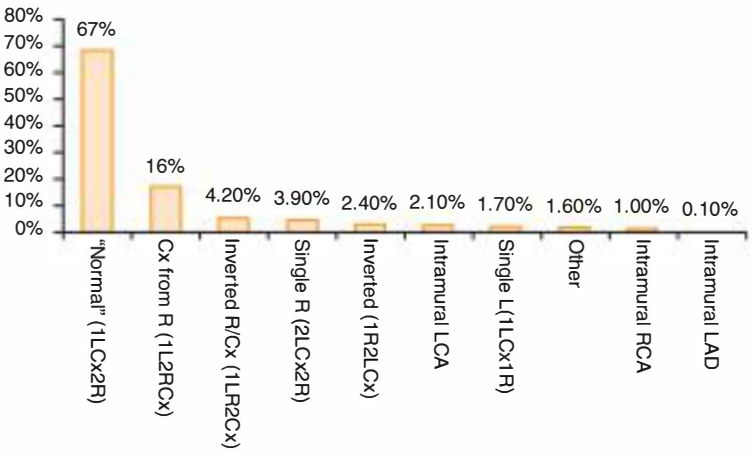



**FIGURE 74-5** Distribution of coronary patterns. (Data from Wernovsky G. Transposition of the great arteries. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ (eds). *Moss and Adams' Heart Disease in Infants, Children and Adolescents,* 6th ed. Philadelphia: Lippincott, Williams & Wilkins, 2001:1033. With permission.)

composed of only the anatomic right-to-left shunted blood. Similarly, the *effective* systemic blood flow (the amount of oxygenated blood reaching the body) is equal to the amount of anatomic left-to-right shunting. There are several potential levels of mixing, including an atrial septal defect (ASD), a VSD, and a patent ductus arteriosus (PDA). In D-TGA/IVS, this is achieved by maintaining a PDA with prostaglandin $E_1$ ($PGE_1$) infusion and ensuring an effective atrial-level communication. This may require performance of a blade or balloon atrial septostomy, a fluoroscopically or echocardiographically-guided method of opening the atrial septum, as described by Rashkind in 1966.[17] Rarely, an open atrial septectomy or temporary mechanical support will be required to stabilize a patient prior to an ASO. In D-TGA/IVS and D-TGA/VSD with mild or no PS, there may be adequate mixing at the atrial and/or ventricular levels to allow for the discontinuation of $PGE_1$. In the presence of significant PS, $PGE_1$ will be necessary to provide sufficient pulmonary blood flow.

For patients escaping early diagnosis, the evolution of the intermediate-term pathophysiology depends on the anatomy. In the majority of patients with D-TGA/IVS, the closure of the PDA with the resultant loss of mixing will lead to severe cyanosis and cardiovascular decompensation. Although they are generally significantly cyanotic, a minority of patients may survive undiagnosed with D-TGA/IVS owing to adequate atrial-level mixing. In these patients, the LV will become deconditioned as it becomes acclimated to ejecting against the low-resistance pulmonary circulation. After 4 to 6 weeks, this deconditioning progresses to the point where an ASO would result in LV failure, as the LV would be abruptly required to assume systemic workloads. These ventricles require reconditioning prior to an ASO, as detailed below.

Patients with D-TGA and a nonrestrictive VSD will have pulmonary overcirculation, as in the case of any patient with a large systemic-to-pulmonary shunt. However, unlike the typical patient with a large VSD, patients with transposition are at significant risk for the accelerated development of pulmonary vascular obstructive disease (PVOD). As early as 2 months of age, 20 percent of patients with D-TGA and a nonrestrictive VSD will have Heath-Edwards grade 3 or greater histologic pulmonary vascular changes.[18] By 12 months, up to 89 percent will have grade 4 changes.[19] Although the LV remains conditioned due to the pressure load from the nonrestrictive VSD, the development of PVOD may preclude anatomic repair. Patients with D-TGA/VSD/PS can have a more benign natural history, as the appropriate degree of PS leaves them well balanced between adequate effective pulmonary blood flow and protection from PVOD. The LV in patients with D-TGA/VSD/PS remains conditioned due to the pressure load of both the VSD and the PS.

## CLINICAL FEATURES

D-TGA is the most common cause of cyanosis in infants and accounts for approximately 10 percent of all congenital cardiovascular malformations.[20] The clinical manifestations of a patient with D-TGA are based upon the amount of intercirculatory shunting of the specific anatomy. In the patient with D-TGA/IVS (or a virtually intact septum), cyanosis is essentially universal. Cyanosis is recognized by nursing or physician staff in 56 percent of neonates within the first hour of life and in 92 percent by 1 day.[21] The remainder of the physical exam is often nondiagnostic. Systolic cardiac murmurs are present in approximately half of the patients, but are usually of grade 2 or less. In the presence of a large VSD, the cyanosis may be very mild and initially overlooked. Signs of congestive heart failure (CHF), including tachycardia and tachypnea, generally become evident by 2 to 6 weeks as pulmonary vascular resistance falls and pulmonary blood flow increases. Murmurs may increase, and other ausculatory findings typically associated with CHF may become evident.

These findings may include a grade III to VI pansystolic murmur, a gallop, a middiastolic rumble, and a narrowly split second heart sound with a prominent pulmonary component. The addition of significant PS leads to diminished pulmonary blood flow and severe cyanosis.

## DIAGNOSTIC MODALITIES

The electrocardiogram (ECG) at birth is generally normal for age. Within the first weeks, abnormal RV hypertrophy with right axis deviation becomes evident with D-TGA/IVS. In the presence of a large VSD, biventricular hypertrophy predominates in the majority of patients, while the axis remains normal in approximately one-third. The chest radiograph (CXR) is often initially normal in D-TGA with IVS or VSD. The classic triad of an egg-shaped heart, mild cardiomegaly, and mildly increased pulmonary vascular markings occurs in only about one-half of patients (Fig. 74-6).[21] With D-TGA/IVS approximately one-half to two-thirds of CXRs demonstrate the classic "egg on a string" sign (globular heart with mild or no cardiomegaly below a narrow mediastinal shadow due to the anteroposterior alignment of the great vessels). The pulmonary vasculature is normal in one-third to one-half of patients and mildly increased in the remainder. Over the first few weeks, cardiomegaly may become more apparent, and the pulmonary vascular markings invariably increase. In the presence of a VSD, the cardiac silhouette is generally noticeably larger and the pulmonary vasculature more prominent than in D-TGA/IVS, as pulmonary vascular resistance falls over the first few weeks of life.

Two-dimensional and Doppler echocardiography is the diagnostic modality of choice. Echocardiography can accurately diagnose the origins of the great arteries arising from the incorrect ventricles. Classically, in a long-axis view, the two great vessels can be seen in parallel rather than wrapping around each other in their normally-related configuration. In the short-axis view, the two semilunar valves, which normally lie in different planes, can be imaged in the same two-dimensional slice, resulting in the "double-barreled shotgun" appearance. Doppler/echocardiography can also accurately diagnose the common associated lesions, including the number, size, and location of VSDs, the degree and cause of LVOTO, and assess the patency of the atrial septum and ductus arteriosus. In addition, coronary anatomy can usually be effectively defined. Cardiac catheterization is rarely required for diagnostic purposes in D-TGA except to define particularly complex coronary anatomy, occasionally to clarify multiple or complex VSDs, and to assess pulmonary vascular resistance or LV pressures in the patient presenting late.

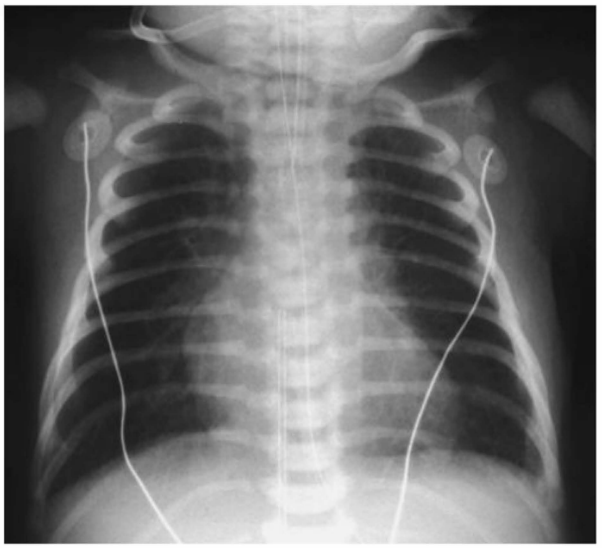


**FIGURE 74-6** Chest radiograph of a patient with D-TGA with intact ventricular septum, demonstrating the classic "egg on a string" radiographic finding.

## MEDICAL THERAPY

Medical management strategies are utilized to palliate the patient until definitive surgical correction can be undertaken. For patients identified at the time of birth or presenting soon thereafter with cardiovascular compromise, $PGE_1$ is instituted to maintain ductal patency. The ASD is examined on Doppler and/or echocardiography. It is essentially always necessary to have a minimally or nonrestrictive ASD to allow adequate mixing. Even in the setting of D-TGA with a large VSD, a significant ASD is usually necessary. This atrial-level shunting is necessary because mixing at the atrial level tends to be more effective, as it occurs in both systole and diastole, unlike the case with a VSD, where shunting occurs primarily during systole. If a restrictive ASD is present, a balloon atrial septostomy is performed under fluoroscopic or echocardiographic guidance. Occasionally, if the atrial septum is particularly thick, a blade and/or static balloon septostomy may be necessary. Rarely is it necessary to proceed with an urgent ASO or an open septostomy for a failed percutaneous intervention. Once a nonrestrictive ASD is identified or created, $PGE_1$ can occasionally be weaned and the PDA allowed to close in D-TGA with a large VSD, while oxygen saturations are closely monitored to ensure adequate intercardiac shunting. This may also be the case for D-TGA/IVS, where atrial-level mixing may be adequate to maintain systemic oxygenation until surgery can be performed.

## SURGICAL THERAPY

In the absence of mitigating factors that would preclude major open-heart surgery—such as poor clinical condition, prematurity, or very low birth weight—our current policy for the treatment of all forms of D-TGA is complete repair in the neonatal period.

## D-Transposition of the Great Arteries Without Pulmonic Stenosis

The current treatment for D-TGA is the ASO, which is performed via a median sternotomy. A portion of autologous pericardium is harvested and placed in dilute glutaraldehyde solution for later use in reconstructing defects created in the proximal aorta where the coronary arteries are removed. Standard techniques of CPB using bicaval cannulation and moderate hypothermia are employed. The arterial cannula is placed slightly higher on the ascending aorta, near the base of the innominate artery, than for other procedures. For straightforward D-TGA/IVS or VSD, deep hypothermic circulatory arrest or low-flow CPB is not necessary. After the initiation of CPB, a left atrial vent is inserted via the right upper pulmonary vein. The antegrade cardioplegia needle is placed in the ascending aorta at the line of planned division or above for later de-airing. The branch PAs are mobilized well past the first order lobar branches. A cross-clamp is applied on the distal ascending aorta and the heart is arrested with antegrade cardioplegia. Interval doses of maintenance cardioplegia may be given throughout the case in a retrograde fashion or administered directly into the coronary ostia. The aorta and main PA are divided (Fig. 74-7A). The PA is translocated anterior to the aorta (Lecompte maneuver) and the distal aorta anastomosed to the proximal PA (Fig. 74-7B). In the technique currently favored at our institution, the neoaorta is reconstructed prior to translocating the coronary arteries. Once the neoaortic anastomosis is completed, the cross clamp can be temporarily removed, allowing the neoaortic root to fill and assume its postrepair three-dimensional shape. We have found that this technique facilitates optimal reimplantation of each coronary artery without tension, kinking, or twisting. The coronary arteries are removed from the aorta

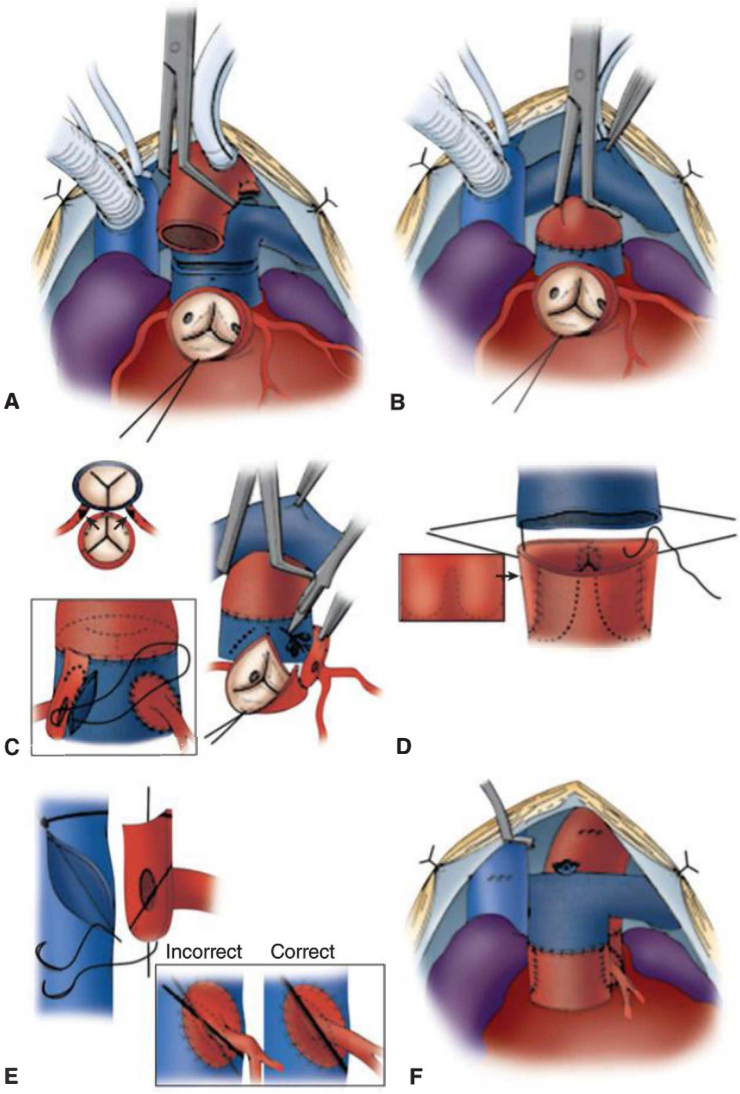



**FIGURE 74-7** The arterial switch operation. **A.** Division of the aorta and pulmonary artery (PA). **B.** The "Lecompte maneuver" with the distal aorta anastomosed to the PA. **C.** Translocation of the coronary arteries. **D.** Reconstruction of the aorta with a pantaloon-shaped patch of autologous pericardium. **E.** Proper alignment of the coronary arteries. **F.** The completed repair. (From Devaney EJ, Ohye RG, Hirsch JC, Bove EL. Congenital heart disease. In: Mulholland MW, Lillemoe KD, Doherty GM, et al. (eds). *Greenfield's Surgery: Scientific Principles and Practice.* Philadelphia: Lippincott, Williams & Wilkins, 2006:1442.)

with buttons of adjacent sinus and transferred to the proximal PA (Fig. 74-7C). The proximal aorta is reconstructed using a pantaloon-shaped patch of autologous pericardium (Fig. 74-7D), and anastomosed to the distal PA. It is important to properly align the coronary buttons in the neoaortic root. As illustrated in Figure 74-7E, the original inferior-most point of the coronary button on the aorta is seldom the same for the new location on the neoaorta. It is imperative to allow the button to sit in the most natural position, which is usually not the same orientation as on the native aorta. The ASD and, if present, the VSD are closed transatrially (Fig. 74-7F).

## D-Transposition of the Great Arteries with VSD and Pulmonic Stenosis

The management strategy of D-TGA with VSD and *significant* PS is determined by the severity and etiology of the PS. Occasionally, in the case of focal subpulmonic stenosis, it may be possible to resect the area of obstruction through the pulmonary valve and proceed with an ASO. However, this resection is technically difficult through the posteriorly located and often hypoplastic pulmonary valve associated with the PS. More commonly, the subvalvar and associated valvar PS precludes an ASO. Although, as mentioned above, our policy is to generally perform complete neonatal repair, there are other options to delay anatomic repair; these may be employed for the management of this particular subset of patients. These strategies are also useful for the patient presenting in poor clinical condition or with prematurity or low birth weight. It is possible for these patients to have well-balanced circulations, with a degree of PS that is significant enough to protect the pulmonary vasculature from the development of PVOD without causing prohibitive levels of hypoxemia. Although the PS tends to be progressive, owing to the continued increase in left ventricular hypertrophy (LVH), it is possible to delay operation in this subset of patients with D-TGA/VSD/PS. Careful monitoring for an increase in cyanosis is, however, imperative. In the presence of severe PS and significant cyanosis, a palliative modified Blalock–Taussig shunt can be performed to delay definitive repair.

Whether performed initially or as a staged procedure, D-TGA in the presence of significant PS and a VSD requires either performance of either a Rastelli or Nikaidoh procedure. The Rastelli operation utilizes the VSD to allow the LV to eject into the aorta. The operation is performed via a median sternotomy with standard aortic and bicaval cannulation. After the initiation of CPB, a left atrial vent and antegrade cardioplegia needle are placed. A cross clamp is applied and the heart is arrested. A right infundibulotomy is performed (Fig. 74-8A). Resection of the infundibular

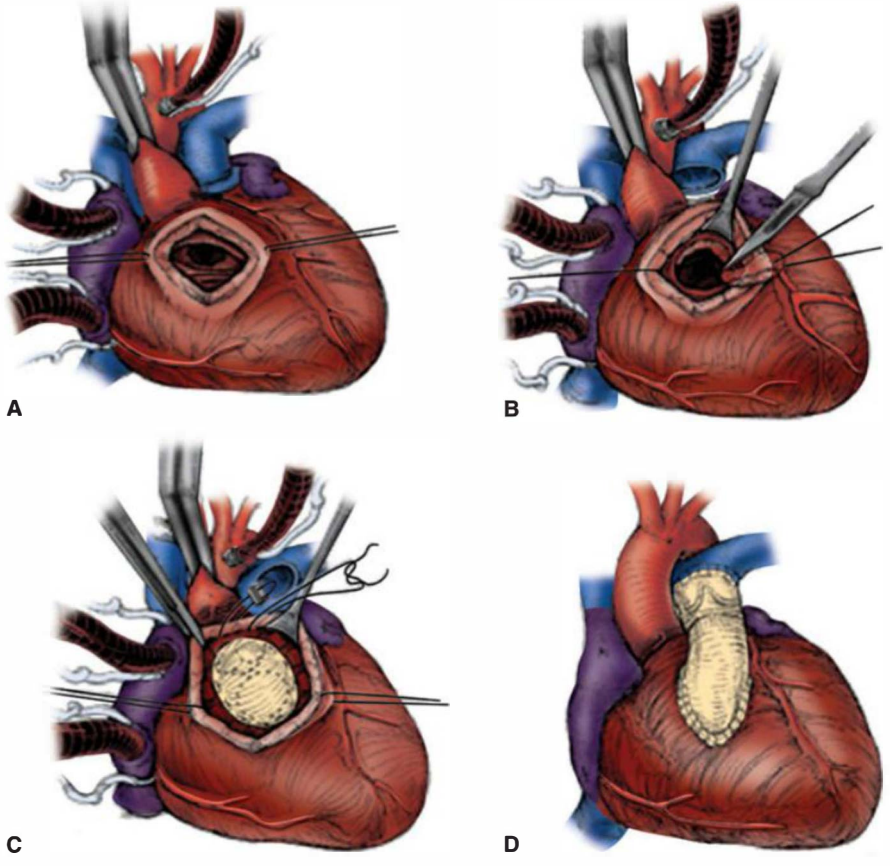



**FIGURE 74-8** The Rastelli procedure. (From Mavroudis C, Backer CL. Transposition of the great arteries. In: Mavroudis C, Backer CL (eds). *Pediatric Cardiac Surgery,* 3rd ed. Philadelphia: Mosby, 2003:465. With permission.)

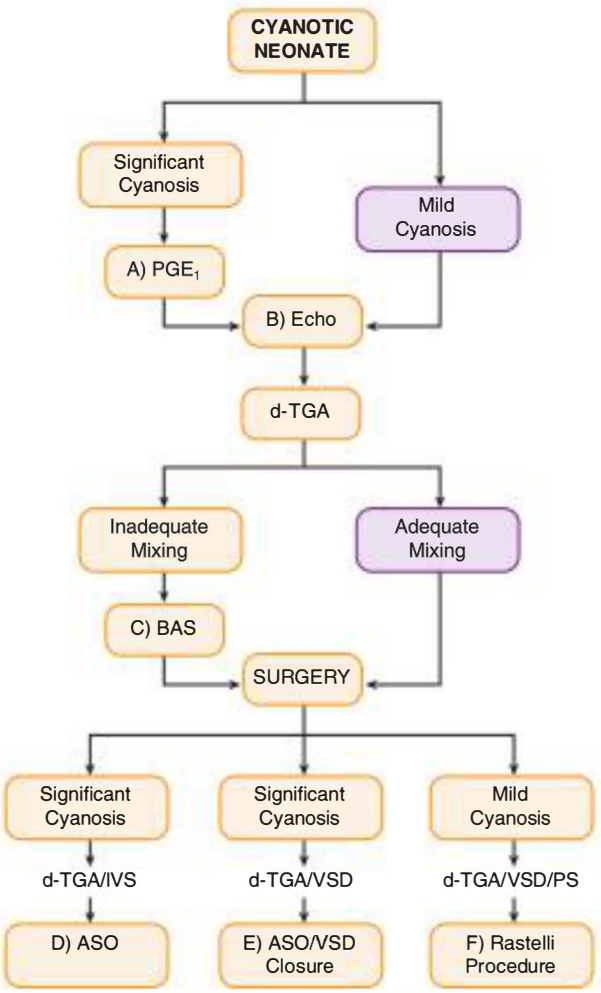



**FIGURE 74-9** Decision-making flowchart.

septum may facilitate the creation of continuity from the LV to the aorta (Fig. 74-8B). The PA is divided at the level of the pulmonary annulus and the proximal end is oversewn. The VSD patch is constructed to incorporate both the VSD and the aortic valve, creating a tunnel from the LV to the aorta (Fig. 74-8C). RV-to-PA continuity is established using a conduit from the RV infundibulum to the distal PA (Fig. 74-9).

The Nikaidoh, or aortic translocation, procedure involves mobilizing the aortic root, either completely or partially leaving a bridge of muscle under the left coronary artery (Fig. 74-10, panels 1 and 3). Standard CPB techniques, as described above for the Rastelli procedure, are employed. The stenotic pulmonary annulus is divided, extending down into the VSD though the conal septum, if present (Fig. 74-10, panel 1). The mobilized aortic root is then sewn into the enlarged pulmonary annulus and the VSD is closed (Fig. 74-10, panels 2, 3, 5, and 6). When aortic root is only partially mobilized, it is pivoted into place in the pulmonary root around the myocardial bridge beneath the left coronary artery (Fig. 74-10, panels 3, 4, and 5). The RCA is reimplanted in this latter technique to prevent excessive tension (Fig. 74-10, panel 5).

## LEFT VENTRICULAR RETRAINING

Because pulmonary vascular resistance falls rapidly during the first days of life, the PA and LV pressures drop. In the absence of a nonrestrictive VSD, significant PS, or large PDA, the LV becomes deconditioned, losing muscle mass and the ability to function at systemic workloads. These LVs require retraining prior to an ASO. The point at which an LV becomes unprepared can be difficult to determine; however, patients presenting after 4 to 6 weeks are certainly of concern. Objective data to make this determination are few, although LV posterior wall thickness or LV muscle mass normal for age suggests that the LV will be able to perform at systemic pressures. For patients with moderate PS or a restrictive VSD, an LV pressure that is 70 percent of the systemic pressure generally indicates a prepared LV. Patients who present with a marginally or clearly unprepared LV require a two-stage approach. The first stage entails the placement of a PA band (PAB) to raise the LV pressure and recondition the ventricle, followed by an ASO. It may also be necessary to add a modified Blalock–Taussig shunt with the PAB to augment pulmonary blood flow. In general, a goal of an LV/RV pressure ratio of 0.7 is desirable. Although this may be achieved in a single banding in patients presenting in the first weeks to months of life, sequential tightening may be necessary in the older patient. Echocardiographic guidance can also be useful during the placement of the PAB to assist in deciding how tight a band will be tolerated. One measure of an effective PAB on echocardiogram is rightward shift of the ventricular septum. The echocardiogram can also be employed to guard against ventricular failure from a PAB that is excessively tight. In patients presenting within the first few weeks to months of life, the retraining process can usually be accomplished within a few weeks. Indications that the LV has been properly reconditioned include an LV/RV pressure ratio of greater than 0.7 and an LV wall thickness or muscle mass that are normal for age.

A particularly challenging group of patients for ventricular retraining are those who present very late or, more commonly, those who present with a failed atrial-level switch. These patients present with RV failure generally associated with severe tricuspid regurgitation. Tricuspid valve replacement has often been unrewarding, as the underlying problem is the RV failure. Among this population of patients, a percentage may be amenable to ventricular retraining. This reconditioning may require several weeks to months, with sequential PAB tightening to achieve a prepared LV. Although similar measures of LV preparedness can be utilized, the determination remains difficult. In addition, many patients may not tolerate the banding and develop biventricular failure. Orthotopic cardiac transplantation remains a viable alternative to ventricular retraining and ASO.

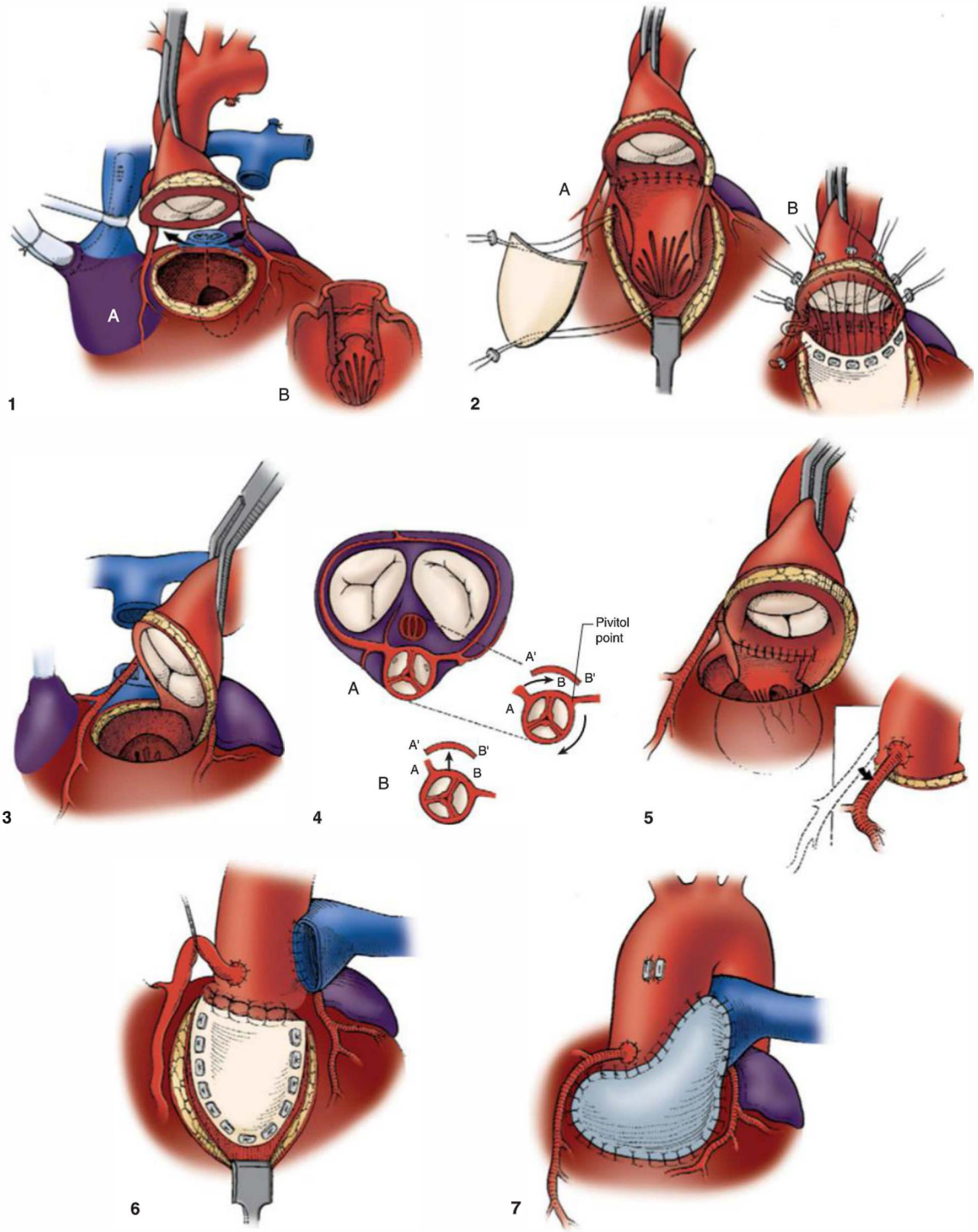



**FIGURE 74-10** The Nikaidoh or aortic translocation procedure. Panel **1A.** The anteriorly located aortic root is fully mobilized (the currently preferred method) and both coronaries are skeletonized. Panel **1B.** Division of the pulmonary annulus and conal septum (when present). Pulmonary–mitral continuity is demonstrated. Panel **2A.** Anastomosis of the aorta to the open pulmonary annulus after posterior translocation. Panel **2B.** Anastomosis of the VSD patch to the anterior rim of the mobilized aortic root. Panel **3.** In the second method of mobilizing the aortic root, partial mobilization of the aortic root is used. A pedicle of myocardium is left intact under the left main coronary artery to decrease the risk of bleeding where the suture lines converge (see Panel **6**). Panel **4B.** The fully mobilized root can shift directly posteriorly without rotation and potentially less distortion of the coronary arteries. Panel **4C.** Partially mobilized roots require rotation of the aortic root around the pedicle of the left main coronary artery. This rotation preserves left main coronary artery alignment, at the expense of the right coronary arterial. Panel **5,** Because of the disproportionate tension on the RCA with partial mobilization and rotation of the root as shown in Panel **4C,** the right coronary artery may require reimplantation. Panels **6** and **7.** The right ventricular outflow tract is reconstructed by anchoring the right lateral wall of the main pulmonary artery to the aortic root and overlaying a patch of pericardium. (From Yeh T Jr, Ramaciotti C, Leonard SR, Roy L, Nikaidoh H. The aortic translocation (Nikaidoh) procedure: Midterm results superior to the Rastelli Procedure. *J Thorac Cardiovasc Surg* 2007;133:461–469. With permission.)

## SPECIAL CORONARY CONSIDERATIONS

Although older series have often identified certain coronary artery patterns, particularly a retropulmonary circumflex or a single left coronary artery from sinus 2 (1L2RCx, 2RLCx, respectively), as risk factors for early mortality, most centers are currently able to perform successful coronary transfers for all arterial patterns.[22–25] Of note, Brown and associates[23] found that the coronary artery pattern was neutralized as a risk factor after switching to the technique of completing the neoaortic anastomosis prior to transferring the aortic buttons, as described above. However, despite these advances, the intramural coronary artery still requires special consideration (Fig. 74-11). Most importantly, the intramural course of the coronary artery must be recognized prior to harvesting the coronary artery button in order to avoid coronary transection. Experienced echocardiographers can usually identify suspicious coronary pathways, but careful intraoperative determination of coronary artery entrance and exit points remains crucial. Once the course of the coronary artery is positively identified, the button can generally be successfully and uneventfully harvested, splitting the aortic wall to elevate valve commissures or cusps as necessary (Fig. 74-12). Unroofing of the coronary orifice might be helpful to ensure a widely patent artery. The two arteries can alternatively be left together and transferred to the neoaorta as a single unit.

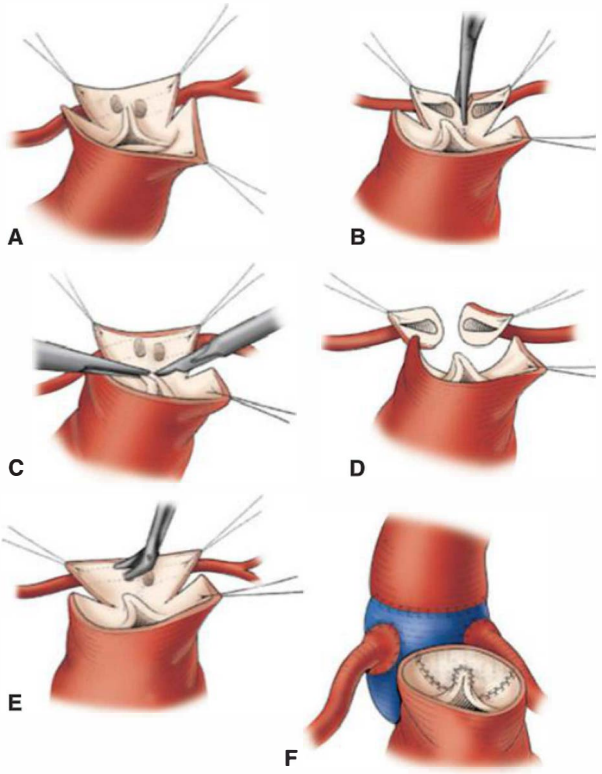



**FIGURE 74-12** The method for coronary transfer of double intramural coronary arteries. **A.** A single button is mobilized. **B.** The commissure is elevated from the aortic wall. **C.** The orifices are unroofed. **D** and **E.** The buttons are excised and divided. **F.** The coronaries are translocated to the neoaorta and the aortic root is reconstructed with autologous pericardium with resuspension of valve commissure. (From Padalino MA, Ohye RG, Devaney EJ, Bove EL. Double intramural coronary arteries in D-transposition of the great arteries. *Ann Thorac Surg* 2004;78:2181–2183. With permission.)

## RESULTS

Currently published hospital survival for the ASO ranges from approximately 90 to 95 percent.[16,23,24,26] D-TGA/IVS has generally a lower mortality than D-TGA/VSD or D-TGA/VSD/PS. Hospital mortality for D-TGA/IVS ranges from 3.5 to 7.6 percent, compared with 9.4 to 13.1 percent for D-TGA/VSD.[23,24] Long-term survival at 5 to 10 years and at 15 years range between 87.9 and 93 percent and 86 and 88 percent, respectively.[23,24,26] The most common cause for reintervention after ASO is supravalvar pulmonic stenosis, occurring in 3.9 to 16 percent.[24,26] A recent study over a 25-year period of 101 patients undergoing a Rastelli operation revealed a hospital mortality of 7 percent, with no deaths in the last 7 years of the study.[27] Actuarial survival at 5, 10, 15, and 20 years was 82, 80, 68, and 52 percent, respectively.

At the C.S. Mott Children's Hospital at the University of Michigan, from January 1999 to January 2004, a total of 114 infants with D-TGA underwent operation. Patients with double-outlet RV or other malformations associated with D-malposition of the great arteries were excluded. Of the 114 patients, 60 had D-TGA/IVS (53 percent); the remaining 54 had D-TGA/VSD (47 percent). Pulmonary

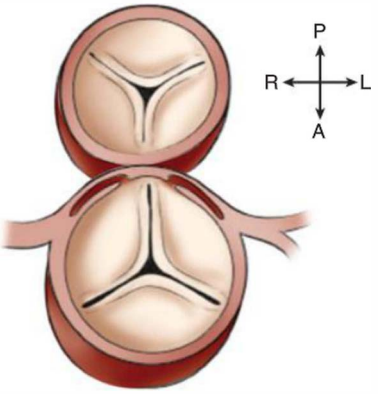



**FIGURE 74-11** An example of double intramural coronary arteries. A, anterior; P, posterior; R, right; L, left. (From Padalino MA, Ohye RG, Devaney EJ, Bove EL. Double intramural coronary arteries in D-transposition of the great arteries. *Ann Thorac Surg* 2004;78:2181–2183. With permission.)

stenosis (PS) was present in 2 patients among those with D-TGA/IVS (3 percent) and in 13 patients with D-TGA/VSD (24 percent). Coronary patterns were 1LCx2R in 75 patients (66 percent), 1L2RCx in 20 (18 percent), and other patterns in 19 patients (16 percent), including 8 intramural coronaries. D-TGA was corrected via a simple ASO in 71 patients (62 percent), ASO with VSD closure in 31 patients (27 percent), and a Rastelli procedure in 12 patients (11 percent). There were two hospital mortalities, both in patients with D-TGA/VSD, for an overall mortality of 1.8 percent. One patient died unexpectedly following an uneventful repair, presumably of cardiac causes, and the second died from necrotizing enterocolitis.

Results for the Nikaidoh procedures were reported by Yeh and colleagues.[28] They described 19 patients undergoing a Nikaidoh procedure at a median age of 3.3 years (range, 0.9–9.3 years) with a median follow-up of 11.4 years (range, 0.1–23 years). There was one hospital mortality due to RCA ischemia, and no late deaths. Five patients have required seven RVOT reinterventions. No patient has required reintervention on the aortic valve or LVOT.

Staged conversion for failed atrial-level switches has been a more challenging problem. In a recent report by Mavroudis and colleagues,[29] 11 patients underwent 15 PA bandings in an attempt at LV retraining; 4 required cardiac transplantation for biventricular failure, 6 have undergone ASO, and 1 awaits conversion. There were no early deaths in the transplanted patients and one late death at 7 years from chronic rejection. There were 2 early and no late deaths in the group undergoing ASO, for an overall successful conversion rate of 40 percent. Overall survival was 64 percent, including the patients awaiting ASO.

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## TRANSPOSITION OF THE GREAT ARTERIES BOARD REVIEW QUESTIONS (CHAPTER 74)

1. Which is correct regarding morphologic classification of TGA?

   A. There is generally situs inversus of the atria.
   B. D-TGA is invariably associated with D-looping.
   C. L-TGA is associated with dextro looping.
   D. L-TGA is also known as simple transposition.
   E. D-TGA is also known as corrected transposition.

2. Which is correct regarding the pathophysiology of TGA?
   A. Deoxygenated blood cycles from the LV to the PA.
   B. The effective systemic blood flow is equal to the amount of anatomic left-to-right shunting.
   C. In D-TGA with IVS, there is no need for $PGE_1$.
   D. If uncorrected, LV deconditioning will occur within 1 to 2 weeks in D-TGA/IVS.
   E. The LV in patients with D-TGA/VSD/PS will become deconditioned within 3 to 6 months.

3. Which is not correct regarding the clinical presentation of TGA?
   A. D-TGA is the most common cause of cyanosis in infants.
   B. Cyanosis is virtually universal with patients with D-TGA/IVS.
   C. Cyanosis is recognized in over 90 percent of neonates within the first 24 h.
   D. Systolic cardiac murmurs are present in 90 percent of infants.
   E. Murmurs may increase over time.

4. Which is not part of the surgical strategy for TGA without PS?
   A. The PA is translocated posteriorly.
   B. The distal aorta is anastomosed to the proximal PA.
   C. The neoaorta is reconstructed prior to translocating the coronary arteries.
   D. The proximal aorta is reconstructed using autologous pericardium.
   E. The VSD is closed transatrially.

5. Which is true regarding outcomes after surgical repair of TGA?
   A. The subset of D-TGA/IVS generally has a higher mortality.
   B. The most common cause for reintervention after arterial switch is supravalvar PS.
   C. Actuarial survival at 10 years for arterial switch is 80 percent.
   D. Actuarial survival at 10 years for Rastelli procedure is 70 percent.
   E. The Nikaidoh procedure eliminates RVOT reintervention.

## ANSWERS

1. **Answer: B.** D-TGA is invariably associated with D-looping. There is generally situs solitus of the atria. D-TGA is also known as simple transposition. L-TGA is associated with L-looping and is known as corrected transposition.

2. **Answer: B.** The effective systemic blood flow is equal to the amount of anatomic left-to-right shunting. Oxygenated blood cycles from the LV to the PA. In D-TGA with IVS, adequate mixing must be maintained by use of $PGE_1$ to maintain ductal patency. LV deconditioning will occur by 4 to 6 weeks in D-TGA/IVS if left uncorrected. The LV in patients with D-TGA/VSD/PS remains conditioned due to the pressure load of both the VSD and PS.

3. **Answer: D.** Systolic murmurs are present in about 50 percent of infants. D-TGA is the most common cause of cyanosis in infants and is virtually universal with an IVS. The cyanosis is recognized in over 90 percent of infants within the first 24 h. Murmurs may increase over time as CHF symptoms develop.

4. **Answer: A.** The PA is translocated anteriorly (LeCompte maneuver). The remaining steps are all standard during the ASO.

5. **Answer: B.** The most common cause for reintervention after arterial switch is supravalvar PS. The subset of D-TGA/IVS has the lowest mortality. Actuarial survival at 10 years after arterial switch is greater than 85 and 80 percent after Rastelli procedure. The Nikaidoh procedure does not eliminate RVOT reintervention.

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# Congenitally Corrected Transposition

*Emile A. Bacha*

***"Corrected transposition, when first encountered, resembles an unreal apparition.... All of the important people were there doing their expert job. The operation began well. The individual cardiac chambers and structures were present and accounted for, and the ventricular septal defect was in the perimembranous location. But something else was fundamentally wrong. Almost everything was out of place in a weird mime of normal, clearly an illusion characteristic of another nightmare. There seemed no choice but to press on even in the face of this confusion, hoping as always that by applying basic principles one could win out. The ventricular septal defect was therefore carefully patched so as to avoid the conduction system, and perfusion was discontinued. Heart block ensued, cardiac output became poor, and tragedy loomed."***

Dwight McGoon, 1983[1]

## KEY CONCEPTS

- Epidemiology
  - Congenitally corrected transposition of the great arteries (CC-TGA) is a rare condition, comprising less than 1 percent of all congenital heart defects.
- Morphology
  - In the most common variety, there is *situs solitus* with discordant atrioventricular (AV) and ventriculoarterial connection (double discordance). Associated anomalies include Ebstein malformation of the tricuspid (systemic) valve, ventricular septal defect (VSD), obstruction of the right ventricular outflow tract, *situs inversus*, and anomalous course of the AV conduction system.
- Pathophysiology and clinical features
  - These are based on the cumulative effects of the associated lesions and the long-term performance of a morphologic right ventricle (RV) facing systemic afterload. Cyanosis and pulmonary overcirculation can ensue, with great variability in the timing of presentation.
- Diagnosis
  - Chest x-ray usually discloses mesocardia.
  - Echocardiography and cardiac catheterization are complementary in determining the necessity and timing of intervention. More recently, cardiac magnetic resonance imaging can be very helpful in determining respective right and left ejection fractions, volumes and help with surgical planning.
- Treatment
  - Some patients may remain asymptomatic, whereas others will only require pacemaker insertion for heart block. Early in infancy, shunting or pulmonary artery (PA) banding (PAB) of symptomatic patients is indicated. Eventually, depending on the timing of presentation and the type of pulmonary outflow, one of three pathways can be chosen: (1) conventional physiologic repair (the RV remains in the systemic circulation); (2) anatomic repair, with recruitment of the morphologic RV and left ventricle (LV) to the pulmonary and systemic circulations; and (3) staged palliation to single-ventricle physiology.
- Outcomes
  - Anatomic repair is technically more challenging but offers the long-term advantage of biventricular physiology. Fontan palliation can be a valid alternative to repair, with acceptable outcomes. Heart transplantation can be indicated in end-stage scenarios (see Chapter 77).

## DEFINITION AND SEQUENTIAL ANALYSIS

The classic definition of "congenitally corrected transposition of the great arteries" (CC-TGA) derived from the observation that the effects of such transposition are "corrected" by the congenital inversion of the two ventricles, with the two circulatory pathways "physiologically" in series despite morphologic derangements. Basically the same as "two negative gives a positive," this condition comprises less than 1 percent of all congenital heart defects.

CC-TGA is created by a "double discordance" between the atria and ventricles on the one hand [atrioventricular (AV) discordance], and the ventricles and the great vessels on the other (ventriculoarterial discordance). Thus, the right atrium is connected through a mitral valve to a morphologic left ventricle (LV), from which the pulmonary artery (PA) arises; conversely, the left atrium is connected via a tricuspid valve (TV) to the anatomic right ventricle (RV), from which the aorta arises. To avoid confusion throughout this chapter, we will try to avoid the use of the terms "left ventricle" and "right ventricle," calling them either morphologically left or subpulmonary ventricle, and morphologically right or subaortic ventricle.

The AV and ventriculoarterial sequence is most frequently associated with a visceroatrial "situs solitus," in which the ventricular loop (see Chapter 59) is located on the left side (L-loop). The concept of "loop" and "handedness" is simplified in Fig. 75-1 by imagining a hand positioned on the convexity of the septum, with the thumb through the AV valve and the index finger through the ventriculoarterial connection. The hand that can be placed with the palm following the convexity of the septum defines the loop. In normally connected hearts, the right hand will be positioned on the septum, the index finger through the pulmonary valve, and the thumb through the TV (D-loop) (Fig. 75-1). L-loop is seen in CC-TGA, where the left hand is positioned on the septum and the thumb goes through the TV (morphology of the AV valve follows and defines that of the underlying ventricle) and the index through the aortic valve.

Rarely, CC-TGA can present with visceroatrial *situs inversus*, with a normal ventricular "loop" (D-loop). The segmental anatomy is then (I,D,D), that is atrial *situs inversus*, D-looped ventricles (normal), and D-transposed great arteries. This type of physiologically corrected transposition (sometimes called "mirror-image" form of (S,L,L) CC-TGA) is often accompanied by additional cardiac malformations such as pulmonary valve stenosis, hypoplastic ventricles and AV valves. Dextrocardia is often seen. Frequently, a single-ventricle approach is necessary in (I,D,D) hearts. This chapter will be dealing with the most common form of corrected transposition, namely (S,L,L) CC-TGA.

The cardiac apex in the most common form of CC-TGA is related to the peculiar position of the anatomic LV, and it is located in a more central position than normal (Fig. 75-2). This location exists even in *situs inversus*, where the cardiac apex is rotated on the right side and more centrally. Heterotaxy is not observed in CC-TGA.

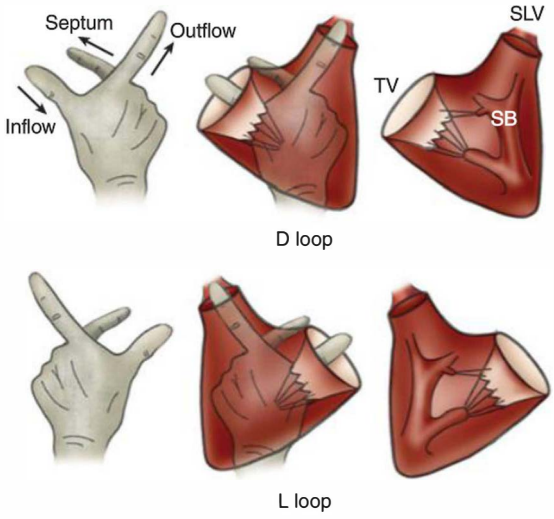



**FIGURE 75-1** Hand topology (loop) in normally connected hearts (D-loop, top) and congenitally corrected transposition (L-loop, bottom). Explanation in text. (From Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott–Raven, 2007. With permission.)

## PATHOPHYSIOLOGY

In isolated CC-TGA, blood from inferior and superior venae cavae and from the coronary sinus drains into the right atrium and then through a bicuspid (mitral) AV orifice into the morphologic LV (physiologic RV, or subpulmonary

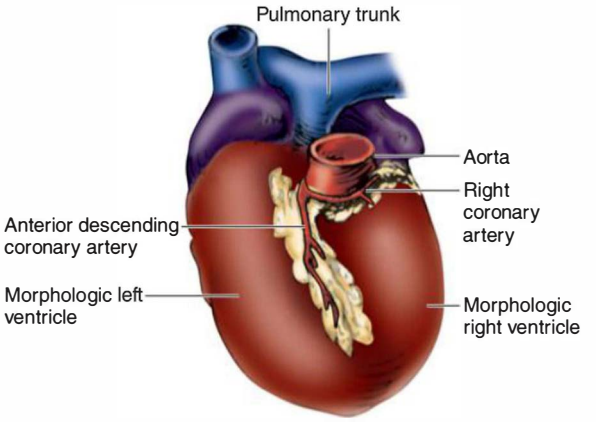



**FIGURE 75-2** Most common external cardiac anatomy in congenitally corrected transposition, with the aorta anterior and to the left, the pulmonary trunk centrally, and mesocardia. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

ventricle). The pulmonary veins drain into the left atrium and blood is transported via the tricuspid AV orifice into the morphologic RV (physiologic LV, or subaortic ventricle). This ventricle pumps the blood into the aorta and therefore into the systemic and coronary circulation. Thus, in CC-TGA, the physiology of the circulation is normal. As a consequence, oxygen saturation within the heart chambers and in the great arteries is normal, even if the blood flows through "wrong" AV valves and ventricles. The PA is in the pathway of the unsaturated blood, while the aorta in the pathway of oxygenated blood. In these hearts one of the most important physiologic aspects that dominates the natural history of CC-TGA is the fact that the morphologic RV has to propel blood into the aorta against systemic resistance and high afterload.

## ASSOCIATED LESIONS

Patients with CC-TGA are usually seen because of the additional lesions that are commonly associated. The most relevant associations are TV regurgitation (the systemic AV valve), often associated with varying degrees of Ebstein malformation of the tricuspid valve, ventricular septal defect (VSD), right ventricular outflow tract obstruction [RVOTO, typically pulmonary stenosis (PS) or atresia], malposition of the cardiac apex, and conduction defects (more frequently complete heart block). The clinical presentation of CC-TGA is dependent on the cumulative effect of associated lesions on pulmonary blood flow. Indication for surgery is also determined by the nature and severity of the associated cardiac defects.[2–4]

## CONDUCTION TISSUE

As mentioned above, the most frequent form of "double discordance" occurs with *situs solitus* and L-loop of the ventricles. The course of the AV conduction tissue therefore differs from that in the normal heart with ventricular D-loop. Although the sinus node is normally located at the superior atriocaval junction, the AV conduction tissue is grossly abnormal. Because of its malalignment with the ventricular septum, the node fails to give rise to a penetrating bundle.[5–8]

In the normal heart, the bundle of His runs in an inferoposterior position with respect to the membranous septum; in SLL CC-TGA, however, the bundle of His is located in an anterosuperior position and has a much longer course than normal. Such a condition poses the risk that the subject with CC-TGA will go on to develop complete AV block, either spontaneously or postoperatively. On the other hand, when CC-TGA presents with *situs inversus* (I,D,D segmental anatomy), the normal anatomic position of the RV (D-loop) allows the bundle of His to follow a normal course. Anderson and coworkers in 1973 first clarified the distribution of the conduction tissue is this anomaly (Fig. 75-3).[8–10]

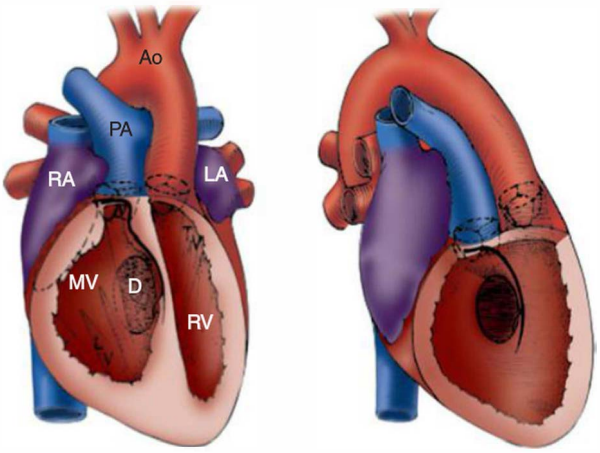



**FIGURE 75-3** Conduction tissue in congenitally corrected transposition with *situs solitus*. The bundle of His courses in a superoinferior trajectory along the leftward margin of the VSD. Ao, aorta; D, ventricular septal defect; LA, left atrium; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; TV, tricuspid valve; conduction system in black.

## DIAGNOSIS AND CLINICAL PRESENTATION

When CC-TGA is isolated (without associated cardiac defects) it can remain totally asymptomatic for life, and the diagnosis is often incidental. The electrocardiogram (ECG) is typical for the absence of a QRS transition complex in the precordial leads. The chest x-ray shows a midline cardiac position in the frontal view, with a linear left upper cardiac border due to the levoposition of the aorta.

The subxiphoid and apical four-chamber echocardiographic views allow identification of the sequential anatomy and visualization of associated ventricular perimembranous defects, valvar and subvalvar pulmonary obstruction, and TV morphology and function.

Cardiac catheterization and angiography and/or cardiac magnetic resonance complete the functional and structural assessment. The clinical presentation depends on the associated defects and pathophysiologic patterns.

In forms associated with a nonrestrictive VSD, pulmonary overcirculation with left-to-right shunting is observed, with elevated pulmonary blood flow (PBF) and various degrees of pulmonary hypertension. In such cases, the infant may present with active precordium, tachypnea, failure to thrive, and recurrent pulmonary infections.

When the VSD is associated with valvular and/or subvalvular PS, progressive cyanosis secondary to right-to-left shunting is seen.

## NATURAL HISTORY

In the isolated form, symptoms may be absent until the sixth or seventh decade of life, and the individual may have a near normal life expectancy. Onset of complete AV block

or systemic AV valve incompetence with congestive heart failure is fairly frequent. However, in atrial *situs inversus*, because of the considerably higher prevalence of a normally positioned AV node, there is less likelihood of the spontaneous development complete heart block. When heart block develops, pacemaker implantation is of course necessary.

## SURGICAL TREATMENT

The surgical history of patient with double discordance can start either with palliative procedures and continue with intracardiac repair or begin with primary complete surgical correction.

### Palliative Procedures

Depending on the initial anatomy (RVOTO, VSD, etc), and on the clinical presentation, many patients first undergo an initial palliative operation such as a systemic to pulmonary shunt, PA band, or even stage I Norwood. If they are not slated for single-ventricle pathway, they receive an anatomic or physiologic intracardiac repair after one or more surgical palliative operations (see below). Correct timing of surgery in such patients is another determining factor of early and late outcome, with the goal of preserving biventricular systolic and diastolic function. If any surgical palliation should be needed before repair, it should aim at obtaining a $Q_p/Q_s$ of approximately 1:1.[11]

In general terms, two major categories can be identified according to the pattern of PBF: (1) those with restrictive PBF and (2) those with unrestricted PBF. Patients with restrictive PBF, depending on the severity of PS, might require surgical palliation at different ages. A systemic-to-PA shunt should be preferred in patients younger than 4 to 6 months. In older patients, a bidirectional superior cavopulmonary anastomosis (Glenn shunt, see Chapter 62) should be the palliation of choice, allowing growth and protection of the pulmonary vascular bed. A bidirectional cavopulmonary anastomosis brings the advantage of dramatically reducing the volume load of the RV to normal values and diverting desaturated blood directly to the lungs, thus increasing effective pulmonary blood flow. Patients with unrestricted PBF have a rather usual clinical presentation, with congestive heart failure during the first months of life and failure to thrive: These are babies with a $Q_p/Q_s$ often greater than 2:1. This represents a significant volume overload, which, in the long run, may impair ventricular function. All these findings indicate the need for surgical intervention early in life. If the great arteries do not show severe discrepancy in size (aorta not too small compared with PA) PA banding (PAB) may represent a good surgical option.

### Intracardiac Repairs

Biventricular repair of CC-TGA is possible, but complete physiologic or anatomic connections are complex and associated with significant long-term problems, such as arrhythmias, subaortic obstruction, valvular dysfunction, obstruction of the ventricular-to-PA conduit, and deteriorating ventricular function. Recent advances have supported a variety of surgical strategies, with outcomes heavily correlated to the experience of the surgeon and institution in which the child is cared for.

### Physiologic Biventricular Repair

Intracardiac repair of VSD in CC-TGA has presented technical problems and has been associated with a high operative risk. Progressive definition of the relative merits of the different approaches to the VSD, the use of conduits in establishing unobstructed flow between the subpulmonary ventricle and the PA, and better knowledge of the anatomic relations of the conduction system to the VSD and pulmonary outflow tract have provided a more favorable basis for physiologic repair of this malformation.

#### VENTRICULAR SEPTAL DEFECT

The approach for VSD closure can be through the right-sided mitral valve, through the aorta, or through the left-sided TV. Exposure of the VSD through a right atriotomy can also be enhanced by partially detaching the leaflet of the right AV valve. In patients in whom replacement of the right AV valve is required, the valve can be excised before VSD closure. If an initial atriotomy gives inadequate exposure, a ventriculotomy on the subpulmonary ventricle may be necessary to allow closure of the defect.

#### RIGHT VENTRICULAR OUTFLOW TRACT

As Anderson and colleagues[12] have indicated, in CC-TGA "as a consequence of malalignment of interatrial, interventricular, and conal septum, the pulmonary outflow tract is an obliquely oriented channel which is particularly prone to obstruction." RVOTO may be at valvular or subvalvular level.[9–15]

It is also to be recalled that in CC-TGA, the abnormal origin of the PA is just posterior to the right coronary artery: The pulmonary outflow tract is wedged deeply into the ventricular chamber between the AV valves. Pulmonary valvular stenosis in the absence of annular hypoplasia is managed by valvotomy. Relief of subvalvular or annular stenosis by direct resection of the conal septum is contraindicated because of the presence of specialized conduction tissue in this region. Patch enlargement of the pulmonary outflow tract is further contraindicated because of the overlying coronary artery. Thus an extracardiac conduit extending from the morphologic LV (pulmonary ventricle) to the PA seems to provide the most effective means for relief of isolated RVOTO.[16]

A particular technique has been developed in order to reduce the risk of heart block in attempting relief of PS in CC-TGA by means of a valved conduit. The VSD is closed

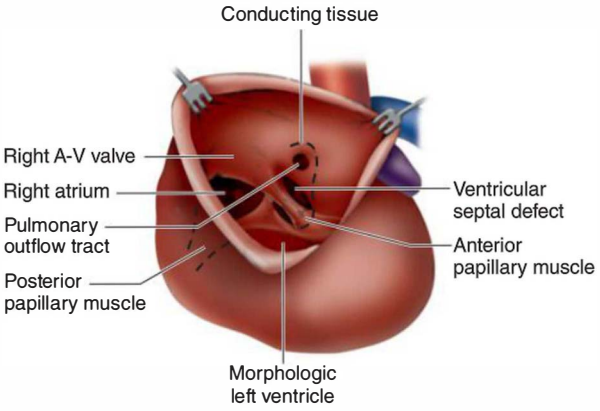



**FIGURE 75-4** Exposure of the VSD through a ventriculotomy (oversized for graphic purposes) in the right-sided morphologic LV. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

with a large patch in such a way that both great arteries and the major conduction bundles lie to the left of the patch. This technique requires use of an extracardiac conduit to reconstruct the RVOT. The procedure is completed by dividing the pulmonary trunk and closing its proximal stump or by ligating it (Figs. 75-4, 75-5, and 75-6).

Despite knowledge of the anomalous location of the conduction system[9,13,16] in CC-TGA, the risk of heart block remains a major concern.[6,17–20] Nevertheless, physiologic repair by means of VSD closure and RVOT reconstruction in patients with CC-TGA/VSD/RVOTO can be recommended with greater optimism than earlier experience would justify.

AV valve malformation was first reported by Edwards.[21] Becu[2] and Allwork[13] have recently demonstrated the high frequency of associated left AV valve anomalies resembling Ebstein malformation (see Chapter 85) and suggest that the morphologic TV is anatomically abnormal in the majority of cases but functionally deficient in only about one-third.[12] Depending on the anatomy encountered, incompetence of one or both AV valves can be managed by valvuloplasty, annuloplasty, or, most frequently, valve replacement.

## Anatomic Biventricular Repair

In patients with AV and ventriculoarterial discordance and following physiologic repair, the morphologic RV and TV may progressively deteriorate while functioning in the systemic circuit. Both the RV and the TV are not designed to be on the systemic side of the circulation. The RV has only one coronary as opposed to the two for a LV. Contrary to the mitral valve, which has no attachments to the septum, the TV subvalvar apparatus is partially based on the septum (muscle of Lancisi and septal papillary muscle), therefore being more susceptible to shifts in the septum. Therefore, the strategy of placing the morphologic LV and mitral valve into the systemic circulation is a better physiological proposition, and can be achieved only by a *double-switch operation*, which has been proposed by Ilbawi and associates[22] and Marcelletti and colleagues.[23] It consists in switching both venous return and arterial outflow. The concept of a double switch was initially suggested for patients with CC-TGA, VSD, and PS and subsequently applied to CC-TGA without PS, with or without VSD.

In this setting, a Mustard or Senning intraatrial transposition of venous return is performed as usual for simple TGA. It is not uncommon for CC-TGA of the S,L,L and I,D,D types to have associated cardiac positioning abnormalities, such as mesocardia or apicocaval juxtaposition. In these cases the free wall of the systemic venous atrium is likely to be deficient, making the Mustard preferable to the Senning technique, because the Mustard entails pericardial patch reconstruction of the atrium.[24]

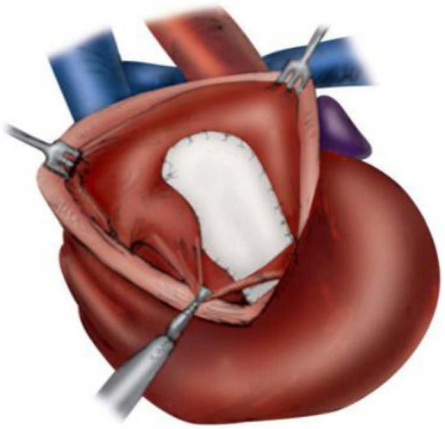


**FIGURE 75-5** The VSD is closed with a patch, then secured anteriorly and to the left away from the conduction system. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

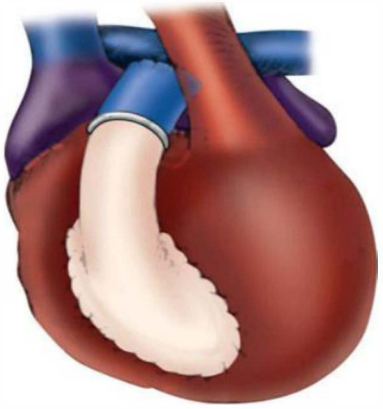


**FIGURE 75-6** A valved conduit is interposed between the subpulmonary ventricle and the pulmonary arterial confluence; the proximal PA stump is then over-sewn. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

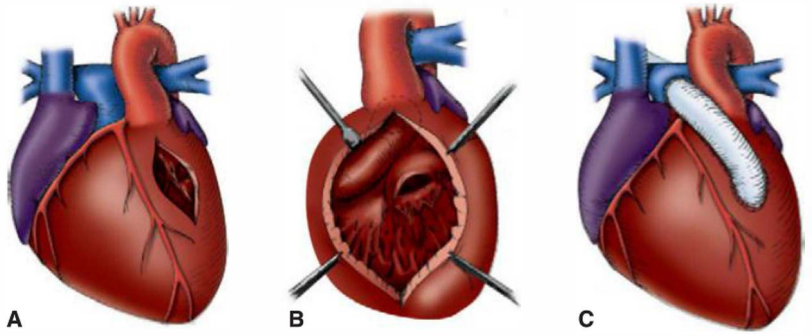



**FIGURE 75-7** Anatomic correction of congenitally corrected transposition with VSD. A subaortic ventriculotomy is made in t he morphologic RV (**A**). A baffle is created, channeling blood from the subpulmonary morphologic RV (**B**). Continuity between morphologic RV and PA is established with a valved conduit (**C**). In cases without *situs inversus*, a Mustard intraatrial baffle is also placed to redirect venous return (not seen in the illustration). (From Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott–Raven, 2007. With permission.)

For patients with VSD and PS, a morphologic LV–to–aortic intracardiac baffle is accomplished through a subaortic incision in the infundibulum of the morphologic left-sided RV. Finally, a LV–to–pulmonary trunk conduit is placed (Rastelli operation, Fig. 75-7).[23]

A connection from the superior vena cava to the PA (Glenn anastomosis) may be associated with a double-switch procedure (in which the pulmonary ventricle is made anatomically and functionally smaller by the intracardiac baffle and ventriculotomy) so as to unload the systemic venous atrium and subpulmonary ventricle. With this approach, the superior limb of the atrial switch is eliminated, the atrial baffle is simplified, the number of atrial suture lines is diminished, and the aortic cross-clamp time is shortened. Furthermore, less sinus node dysfunction and atrial dysrhythmias can be expected.[27]

For patients without PS, a classic arterial switch operation is performed (see Chapter 74). If a VSD is present, it is closed as described previously. When these procedures are considered for patients without VSD, in whom the morphologic LV is working at low pressure, preparation of the LV for systemic workload can be done by progressively increasing afterload by means of a PA band (ventricular retraining).

When severely unbalanced ventricles exist and a biventricular repair is not reasonable, a single-ventricle repair is indicated. Also, in case of straddling AV valves or an uncommitted VSD, a single-ventricle approach is preferable to complex biventricular repair.[11] The Fontan principle is, even in the best of circumstances, a palliative one, although most biventricular repairs requiring a valved conduit are palliative as well. A biventricular repair has the advantage of maintaining normal physiology, thus leading to better exercise tolerance and fewer atrial arrhythmias. In physiologic terms, the incorporation of a ventricle in the pulmonary circulation allows lower central venous pressure and better adaptation to exercise. There are situations in which the short- and intermediate-term results after a complex biventricular repair have been suboptimal. In such cases, the application of the Fontan principle, even in the presence of two well-balanced ventricles, may improve results.

## Physiologic Versus Anatomic Repair: Controversies and Future Guidelines

There is currently a tendency to prefer the anatomic repair (double-switch procedure). The fact that anatomic repair was first described for CC-TGA with PS is not surprising since in that situation, the LV is exposed to systemic pressures all along, without deconditioning. Thus, LV retraining, one of the major issues for CC-TGA with intact ventricular septum and no PS, is not an issue. The principles of the correction are as follows: (1) rerouting of venous flows at the atrial level; (2) patch closure of the VSD through a right ventriculotomy, baffling the LV to the aorta; and (3) conduit interposition between the morphologic RV and the PA.

If the VSD is restrictive, it can be safely enlarged by extensive resection of the anterosuperior border because of the posteroinferior location of the His bundle in the presence of *situs inversus*. With this technique, the morphologic LV and the native mitral and aortic valves are recruited for systemic work, with intrinsic long-term advantages. It is, however, a complex procedure involving substantial use of prosthetic material. Recent experience suggests that, in the appropriate patient, this approach is superior to the physiologic repair.[25–27]

Physiologic repair of CC-TGA (leaving the morphologic RV in support of the systemic circulation) has been accomplished by different techniques of VSD closure combined with relief, or bypass, of associated RVOTO. Although TV anomalies resembling Ebstein anomaly are not prevalent in *situs inversus*, this approach is potentially frustrated by progressive RV failure and ensuing complete heart block. Accelerating tricuspid regurgitation (TR) is often seen after VSD closure. Thus, one could argue that a "good" Fontan operation may be a better choice than a physiologic repair.

The main theoretical advantage of anatomic correction (double switch or Senning–Rastelli) arises from its use of the LV as the systemic pumping chamber and of the mitral valve

as the systemic AV valve. Performance of an anatomic correction should be strongly considered for patients with TR before surgical intervention, Ebstein malformation of the TV, and RV dysfunction. Heart transplantation remains another option for this difficult patient population but is associated with the drawback of immune suppression. Systemic RV and TV dysfunction (especially if requiring valve replacement) predicts a poor prognosis for many of these patients.

## VENTRICULAR RETRAINING IN THE DECOMPENSATED LEFT VENTRICLE

Ventricular retraining of a decompensated LV is achieved using gradual main PA obstruction by banding. Often, several steps of tightening are necessary, as the LV will not tolerate a sudden jump to near-systemic pressures. Results in older children and adolescents have been disappointing, and typically, a patient should be less than 15 years old. The younger the patient, the better the outcome. Banding is performed under transesophageal echocardiographic guidance, while observing the septal position and measuring LV pressure directly with a needle. If TR has developed with still acceptable RV function, placing a PA band will often reverse the septal shift, thus allowing the septal papillary muscle of the TV to come closer to the other two with improvement in TR.[28] The time of when the LV is ready for taking on all systemic work after a double switch is another difficult clinical question. Typically, it takes at least 6 to 18 months. A catheterization is performed and at least two-thirds systemic pressure with good ventricular function is required. Ventricular wall thickness is also a critical factor, and can be seen on magnetic resonance imaging (MRI) (indexed LV mass to LV volume ratio above 1.5).[27] The largest experience to date is from Dr. Roger Mee's at the Cleveland Clinic.[29]

## THE ASYMPTOMATIC PATIENT WITH CC-TGA

Every so often, one is confronted with a young patient, usually less than 7 years old, with incidental discovery of CC-TGA, intact ventricular septum, and no more than mild TR. The TV may be slightly abnormal. This is a difficult decision-making situation. On one hand, it is impossible to predict who will develop symptoms, and there are reports of individuals who died at an old age with incidental discovery at autopsy of CC-TGA.[30] On the other, development of symptoms usually predicts severe changes, and places the patient in a much higher surgical risk category. Finally, passing the 10 to 15 year of age mark means that ventricular retraining will become much harder if not impossible. Our approach has been to not operate on asymptomatic young patients with no more than mild TR and a well-formed tricuspid valve. We recommend very close cardiology follow-up, and a complete review of the anatomy with MRI also at around age 7. Should the TR progress, even in the absence of symptoms, we recommend embarking on LV retraining and, eventually, the double-switch procedure especially if the TV is morphologically abnormal. This recommendation is bolstered by the fact that development of TR usually precedes RV dysfunction, which is very difficult to manage.[31]

## THE OLDER PATIENT WITH TRICUSPID REGURGITATION

A particular problem seen with more frequency is the case of an adult with recently diagnosed CC-TGA and severe TR in conjunction with RV (subaortic ventricle) dysfunction. Symptoms are exactly the same as those observed in an adult with severe mitral regurgitation and LV dysfunction. It is recommended to proceed to TV replacement early, prior to onset of significant RV dysfunction. Heart transplantation is a good option for end-stage cases. Patients with significant systemic ventricular dysfunction requiring TV replacement are at high operative risk.[31,32] TV repair is not recommended in those cases.

## CONCLUSION

In conclusion, the management of CC-TGA should proceed as follows:

1. Postponement of surgery until the patient becomes symptomatic. AV block remains a risk factor before, during and after surgery.
2. Anatomic repair is preferred. If the LV is under systemic pressure (presence of VSD and/or pulmonary outflow tract obstruction), then a double-switch procedure or an atrial switch with RV–PA conduit is preferred. Recently, aortic translocation with atrial switch has been successfully employed for this subset. If the LV is decompensated, then LV retraining is needed. LV retraining works best in prepuberal patients, and long-term outcomes, even after initial successful LV retraining and double-switch, have been mitigated in terms of late LV dysfunction.[33] Other palliative steps include systemic-to-PA shunt and bidirectional cavopulmonary anastomosis, depending on the age, anatomy, and hemodynamic status.
3. When one or more of the mentioned risk factors would make anatomic correction prohibitive, single-stage palliation should be considered as a preferred alternative to anatomic repair.

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## CONGENITALLY CORRECTED TRANSPOSITION BOARD REVIEW QUESTIONS (CHAPTER 75)

1. Which of the following is not typically associated with CC-TGA?
   A. Ebstein anomaly
   B. VSD
   C. PS
   D. Supravalvar aortic stenosis
   E. Complete heart block

2. Which of the following is correct regarding conduction tissue in CC-TGA?
   A. The sinus node is abnormally positioned.
   B. The AV conduction tissue is grossly normal.
   C. The bundle of His is anterosuperior to the membranous septum.
   D. There is usually a much shorter course of the His bundle.
   E. In *situs inversus*, the bundle of His is remote from the membranous septum.

3. Which is not an appropriate palliative procedure for CC-TGA?
   A. Systemic–pulmonary shunt
   B. Stage I Norwood
   C. PA banding
   D. Balloon septostomy
   E. Bidirectional Glenn shunt

4. Which is correct regarding physiologic biventricular repair?
   A. A ventriculotomy in the subaortic ventricle may improve exposure of the VSD.
   B. Pulmonary valvular stenosis is managed by valvotomy in the absence of annular hypoplasia.
   C. Relief of subvalvular or annular stenosis is best addressed through direct resection of the conal septum.
   D. Patch enlargement of the pulmonary outflow tract should be routinely performed.
   E. The VSD is closed to place the great arteries and conduction system to the right of the patch.

5. Which of the following is not performed during an anatomic biventricular repair?
   A. An intraatrial switch
   B. An LV to aortic intracardiac baffle in the setting of VSD and PS
   C. A Rastelli procedure
   D. A Glenn anastomosis
   E. An extracardiac Fontan procedure

## ANSWERS

1. **Answer: D.** Ebstein anomaly, VSDs, RVOTO, and conduction defects are all associated with CC-TGA; supravalvar aortic stenosis is not.

2. **Answer: C.** The bundle of His typically is located anterosuperior to the membranous septum. The sinus node is normally positioned, but the AV conduction tissue is grossly abnormal due to its malalignment to the membranous septum. The His bundle has a much longer course than normal. In *situs inversus*, the bundle of His follows a normal course.

3. **Answer: D.** Intracardial mixing is not the underlying pathophysiologic problem in CC-TGA, and therefore balloon septostomy is not indicated. Palliative procedures for ccTGA focus on either increasing or limiting pulmonary blood flow, depending on the clinical setting.

4. **Answer: B.** Pulmonary valvular stenosis is managed by valvotomy in the absence of annular hypoplasia. Improved exposure of the VSD can be obtained by ventriculotomy in the subpulmonary ventricle, and the VSD is closed to place the great arteries and conduction system to the left of the patch. Direct resection of the conal septum is contraindicated to avoid damage to the conduction system. Patch enlargement of the pulmonary outflow tract is also contraindicated to avoid coronary artery injury.

5. **Answer: E.** During an anatomic biventricular repair, both atrial and ventricular procedures are required (double-switch operation). An intraatrial switch (Mustard or Senning procedure) is combined with either a classic arterial switch or an intraventricular baffle and Rastelli procedure. A Glenn anastomosis can be used to unload the systemic atrium and ventricle. An extracardiac Fontan procedure is not typically performed, as this is used for patients with single-ventricle physiology.

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# 76 Hypoplastic Left Heart Syndrome

*Peter J. Gruber*
*Thomas L. Spray*

## KEY CONCEPTS

- Epidemiology
  - Hypoplastic left heart syndrome (HLHS) accounts for 5 percent of all congenital heart anomalies and is responsible for 25 percent of cardiac deaths in the first week of life. Its incidence is 1.8 in 10,000 live births, with 25 percent of cases showing associated noncardiac malformations and 5 percent associated with chromosomal abnormalities.
- Morphology
  - HLHS includes a wide spectrum of anatomic abnormalities with the common feature of hypoplasia of the left ventricle (LV) and the ascending aorta. At one end of the spectrum there may be some mild LV hypoplasia, mild aortic stenosis, and aortic coarctation. At the other end there is complete absence of the LV, aortic atresia, and aortic arch interruption.
- Pathophysiology
  - Systemic venous return is channeled via an interatrial communication to the right ventricle (RV) and, through the pulmonary artery (PA) and patent ductus arteriosus (PDA), to the systemic and pulmonary circulations. Balanced physiology ensues, with $Q_P$:$Q_S$ varying according to systemic and pulmonary vascular resistance (PVR) as well as with the unrestrictive nature of the atrial septal defect (ASD).
- Clinical features
  - As a result of ductal closure in the postnatal period, HLHS is uniformly fatal if not treated. Evidence of pulmonary overcirculation is evident on clinical examination once PVR diminishes in early post-natal life.
- Diagnosis
  - Prenatal echocardiography can be used to detect unbalanced ventricles as early as 20 weeks of gestational age. Postnatal echocardiography readily establishes the diagnosis and guides medical and surgical decision-making.
- Treatment
  - Prostaglandin $E_1$ ($PGE_1$) infusion is the cornerstone of early resuscitation, coupled with balloon atrial septostomy in case of a restrictive ASD. A three-stage single-ventricle palliation approach has been adopted by most centers. The first stage involves aortic arch reconstruction and establishment of a reliable source of pulmonary blood flow, and the second and third stages consist of sequential partitioning of the systemic and pulmonary circulations. Transplantation has been used as the initial approach or, more commonly, for those who fail palliative strategy. In high-risk neonates, initial palliation with a hybrid approach (stenting of coarctation and PA banding) should be considered.
- Outcomes
  - Operative survival of stage I Norwood palliation depends on several variables, including anatomic factors (diameter of ascending aorta, operative weight, restrictive ASD, associated anomalies), and nears 80 percent in several series. Operative mortality between 5 and 10 percent has been observed for second- and third-stage palliation. Long-term complications [ventricular failure, atrioventricular (AV) valve regurgitation, arrhythmias, and protein-losing enteropathy, among others] dictate late prognosis and the need for reintervention or transplantation.

## DEFINITION

Hypoplastic left heart syndrome (HLHS) is a challenging disease that includes a wide spectrum of anatomic abnormalities with the common feature of left ventricular (LV) hypoplasia and hypoplasia of the ascending aorta. At one end of the spectrum there may be mild (LV) hypoplasia, mild aortic stenosis, and aortic coarctation. At the other end of the spectrum, there may be complete absence of the LV, aortic atresia, or an association with interrupted arch. All these neonates present a serious challenge to congenital heart surgeons, cardiologists, anesthesiologists, critical care specialists, nurses, and families. HLHS is uniformly fatal in the absence of intervention. There is now little argument about the utility of staged operative repair in these children as a result of continued improvements in operative techniques and perioperative care.

## HISTORICAL HIGHLIGHTS

Therapy for HLHS has been one of the great successes in the treatment of congenital heart disease (CHD). Before the 1980s, HLHS was a uniformly lethal condition. Over the past 30 years, palliation of HLHS has become a standard operation in nearly all institutions. In 1952, Lev[1] first described maldevelopment of the left-sided cardiac structures in combination with a small ascending aorta and transverse arch. By 1958, Noonan and Nadas had further defined the syndrome to include a variety of cardiac malformations of left heart structures.[2] The first report of any attempt to palliate a patient with mitral atresia was in 1961 by Redo and associates, who performed an atrial septectomy using inflow occlusion through a right thoracotomy; the patient died soon after the operation.[3] In 1968, Sinha and coworkers outlined management principles that remain in use today that include creation of an unobstructed atrial communication, unrestrictive systemic flow, and control of pulmonary blood flow.[4] Cayler and colleagues described an anastomosis between the right pulmonary artery (PA) and the ascending aorta with banding of both right and left PAs.[5] Interestingly, 40 years later, PA banding is being employed for selected children in whom medical conditions or anatomic substrates render them unsuitable for stage 1 Norwood reconstruction. This first-stage hybrid procedure involves stenting the ductus arteriosus and atrial septal defect, with placement of bilateral PA bands.[6,7] Litwin, Mohri, and others all performed unsuccessful operations that were variations of these principles, which nevertheless contributed to the development of the knowledge of the disease and its palliation.[8,9] In 1977, Doty and Knott described primary reconstruction that included atrial septation and a right atrium (RA)-to-PA Fontan circuit.[10] Again, though no patients survived, this experience confirmed that one-stage reconstruction would not be successful because of high neonatal pulmonary vascular resistance (PVR). Levitsky, Behrendt, and others described multiple, possible surgical procedures.[11,12] Although the procedures demonstrated no long-term success, they established the principle of staged reconstruction as first described for tricuspid atresia by Fontan and Kreutzer. This included a strategy of initial palliation followed by eventual separation of the systemic and pulmonary circulations.[13,14] However, it was William Norwood who provided the seminal contribution in 1980 and in 1983, with the first report of a successful staged approach.[15,16] The Norwood procedure remains the primary reconstructive approach to this day.

## EMBRYOLOGY AND ANATOMIC CONSIDERATIONS

From a molecular standpoint, the developmental mechanisms that underlie HLHS remain obscure, although steady progress continues.[17] Multiple genetic loci are associated with HLHS including the chromosomal abnormalities of trisomy 13 and 18, Turner (XO), and Jacobson (11q deletion) syndromes. Single gene defects with potential associations include GJA1,[18] NKX2-5,[19] NOTCH1,[20] and HAND1.[21] Furthermore, using a genome wide linkage approach, two loci (10q and 6q) have been associated with HLHS, suggesting that new technologies may provide important information.[22] Embryologically, there are additional clues. The severe hypoplasia of left heart structures is associated with, and likely a consequence of, limited flow during development secondary to a primary abnormality of either LV inflow or outflow. Primary defects of myocardial growth are unlikely to be a mechanism for this disease, since the myocardium appears normal.[23,24] In addition, in approximately 5 percent of patients with aortic atresia, an unrestrictive ventricular septal defect coexists and, in such cases, there is nearly always normal development of the LV and mitral valve.

Patients can be categorized on the basis of atrioventricular (AV) and semilunar valvular morphology into three primary subsets: (1) aortic atresia with mitral atresia (40 percent), (2) aortic stenosis with mitral stenosis (30 percent), and (3) aortic atresia with mitral stenosis (30 percent) (Fig. 76-1). Aortic stenosis with mitral atresia is rare. HLHS variants include a malaligned AV canal; double-outlet right ventricle (RV) with mitral atresia; tricuspid atresia with transposed great arteries, and a univentricular heart with aortic stenosis. There is frequently leftward and posterior deviation of the septal attachment of septum primum, but this is unlikely to be a common developmental mechanism, since it is seen commonly in other CHD patients. Usually, the superior and inferior venae cavae (SVC and IVC) are connected normally to the RA, although in about 15 percent of patients a left SVC draining to the coronary sinus is present. Other structural abnormalities of the heart are rare, with less than 5 percent of patients demonstrating valvular dysplasia. Also rare (less than 5 percent) is the association with abnormalities of pulmonary venous return or interruption of the aortic arch. Abnormalities in brain development have been reported

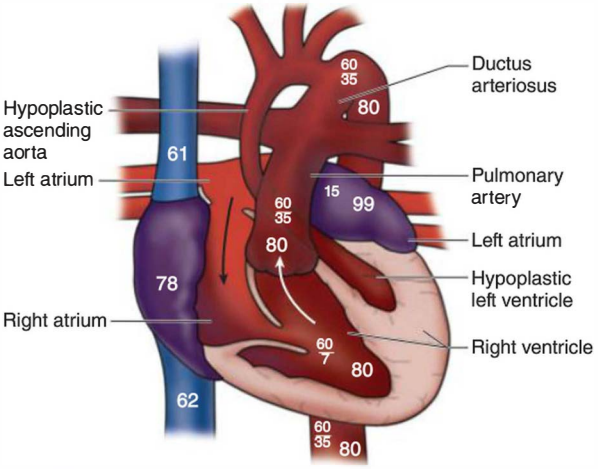



**FIGURE 76-1** Anatomy and physiology of hypoplastic left heart syndrome. Hypoplastic left-sided structures force pulmonary venous blood to flow from the left atrium through the interatrial communication to the right atrium (downward arrow). Blood from the right ventricle flows both to the pulmonary circulation via the pulmonary artery (upward arrow) and to the systemic circulation via the ductus arteriosus. Maintenance of ductal patency is critical for survival. The surgical principles of repair aim at maintaining this stable physiology. (Reprinted with permission from Gruber P, Spray T, et al. Hypoplastic left heart syndrome. In: Kaiser LK, Kron IL (eds). *Mastery of Cardiothoracic Surgery*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2007:936.)

with increasing frequency in children with severe CHD, and may define a high-risk group for operative repair.[25] The pulmonary vascular tree also harbors abnormalities, with an increase in number and muscularity of vessels.[26,27]

## PATHOPHYSIOLOGY

A normal fetus has a parallel circulation that adequately supports single-ventricle physiology before birth. Three communications (the ductus venosus, foramen ovale, and ductus arteriosus) shunt oxygenated placental blood largely past the hepatic and pulmonary beds to supply the splanchnic circulation. HLHS is well supported in this situation and, as a result, it is rarely a cause of fetal demise. HLHS may be a secondary result of early obstructive lesions of either mitral or aortic valvular development, and this hypothesis has been supported in animal models of mitral or aortic stenosis with resulting LV hypoplasia.[24] However, the primary cause of the obstructive flow lesion that may secondarily lead to HLHS is unknown. Interestingly, there are no known genetic animal models that recapitulate HLHS despite the existence of a large number of mutations that affect valvular development. This argues for a complex early multifactorial event or a transient early insult.

## EPIDEMIOLOGY

HLHS is a uniformly fatal disease if untreated. It represents 5 percent of all cases of CHD and is responsible for nearly 25 percent of cardiac deaths in the first week of life. Among 10,000 live births, approximately 1.8 are born with HLHS, with a slight male predominance. Of these, 25 percent will also have a noncardiac anomaly, and 5 percent a chromosomal abnormality (most typically trisomy 13, 18, or 21). Syndromic lesions are rare but, among these patients, Turner syndrome (monosomy X) is the most common. The recurrence risk is 2.2 percent for one affected sibling and 6 percent for two affected siblings, suggesting a genetic predisposition but arguing against a simple effect.

## CLINICAL PRESENTATION

The presentation of infants with CHD has changed dramatically over the past 15 years. In most large centers, the majority of patients are identified through prenatal echocardiography; this early identification has not been correlated consistently with a better outcome. Although some tachypnea and mild cyanosis may be present, it is not until the ductus arteriosus begins to close that children with HLHS manifest evidence of impaired systemic perfusion with pallor, lethargy, and diminished femoral pulses. Cardiac examination reveals a dominant RV impulse, a single second heart sound, and often a nonspecific soft systolic murmur. Electrocardiographic examination reveals RA enlargement and RV hypertrophy. Chest x-ray occasionally shows mild cardiomegaly and increased pulmonary vascular markings.

## DIAGNOSIS

Physical examination of children with HLHS is usually normal. The examination is determined by the underlying anatomy as well as the chronicity of the disease (ductal closure and PVR). Poor perfusion, weak distal pulses that may not be present because of the size of the ductus, acidosis, and a sepsis-like picture may confound the diagnosis. In the absence of risk factors or laboratory findings consistent with sepsis, one should look for left-sided obstructive lesions.

There are no specific laboratory indicators of HLHS. These patients usually exhibit normal values. With ductal closure and malperfusion, end-organ compromise may be reflected by evidence of metabolic acidosis as well as altered hepatic and renal function tests.

At 20 weeks of gestation, a fetal echocardiogram has reasonable visualization of the cardiac structures. It is, however, neither feasible nor cost-effective to screen all pregnancies. Therefore, a selective approach is currently taken by which only mothers at high risk are screened. Ventricular size discrepancy is frequently the first hint of impending problems. Certainly, the presence of an intact or restrictive atrial septum should prompt term high-risk delivery in an institution

where an urgent postdelivery atrial septectomy or catheter-based septostomy and atrial stenting can be rapidly performed. The use of prenatal screening improves the prenatal condition of the child but may not translate into an improved outcome (at least in cases of transposition of the great arteries or HLHS).[28,29] After delivery, the infant should undergo two-dimensional and Doppler echocardiography to define anatomy to an extent sufficient for medical and surgical decision-making. It is important to distinguish HLHS from other diseases that may mimic certain of its features, as their management may differ substantially.

Chest radiography often demonstrates mild cardiomegaly and excessive pulmonary blood flow. A head ultrasound should be obtained in all patients to rule out intracranial hemorrhage and minimize the risks of heparinization. Patients with medical necrotizing enterocolitis should have a course of intravenous antibiotics before first-stage palliation.

## MEDICAL THERAPY

Regardless of the anatomic subtype, preoperative stabilization is critical to the ultimate outcome of patients with HLHS. Nearly all patients with suspected HLHS are transported on prostaglandin E1 ($PGE_1$) at a dose of 0.01 to 0.025 μg/kg/min. Two clinically dose-dependent side effects of $PGE_1$ are hypotension and apnea, though they are infrequently clinically significant. Umbilical arterial and umbilical venous lines are used for monitoring and central access in most patients. Most infants can ventilate with a natural airway and indeed will often have more favorable hemodynamics while extubated. Supplemental oxygen should generally be avoided, as it will act as a pulmonary vasodilator, decreasing PVR, increasing $Q_p$:$Q_s$, and thus decreasing systemic perfusion. Inotropic support is required in patients who have had a perinatal insult, but is otherwise rarely necessary. The goal of these maneuvers is to get the patient to the operating room as stable as possible.

## SURGICAL THERAPY

There are two primary therapies for HLHS: (1) staged reconstructive surgery leading to a modified Fontan–Kreutzer procedure and (2) heart transplantation. Heart transplantation is discussed in detail in Chapter 89; this chapter focuses on staged reconstructive surgery.

Over the past 25 years, the Norwood procedure has evolved to become the standard approach in nearly all institutions that care for neonates and infants HLHS. There are three primary goals of first-stage palliation: (1) establishment of unrestricted interatrial communication to provide complete mixing and avoidance of pulmonary venous hypertension, (2) establishment of reliable source of pulmonary blood flow, allowing for the development of pulmonary vasculature and for the minimization of the volume load on the single ventricle, and (3) provision of unobstructed outflow from the ventricle to the systemic circulation. Most institutions will offer surgical palliation to nearly all patients with HLHS, very low-birth-weight infants, and those with nonlethal genetic syndromes.

### Stage I Reconstructive Procedure

Two perfusion techniques can be used for first-stage palliation: deep hypothermic circulatory arrest (DHCA) and selective antegrade continuous cerebral perfusion. At present, there is no consensus on the superiority of one approach over the other.[30]

The child is brought to the operating room and ventilated on room air, with care taken to avoid hyperventilation. A full midline sternotomy is performed, and the thymus is removed in its entirety, with care being taken to avoid the phrenic nerves. The pericardium is opened and an obligatory mediastinal inspection is performed to confirm the echocardiographic findings and, in particular, to identify abnormalities of the aortic arch and coronary arteries. The ascending and descending aorta, head vessels, ductus arteriosus, and PAs are mobilized extensively with care taken to preserve the integrity of the recurrent laryngeal nerve. No attempt is made to dissect the systemic veins. Purse-string sutures are placed in the proximal main pulmonary artery (MPA) and generously around the RA appendage, through which heparin is administered. A previously thawed pulmonary homograft hemiartery patch is trimmed in an extended arrowhead shape and set aside.

After the activated clotting time reaches 300 seconds, the patient is cannulated, with the arterial cannula inserted at the base of the MPA and a single venous cannula inserted in the RA (Fig. 76-2). Cardiopulmonary bypass (CPB) is initiated, and snares are brought down around the branch PAs. The patient is cooled to 18°C over 15 min, during which time any remaining dissection is performed. A side-biting clamp is placed on the innominate artery, and a Gore-Tex graft (usually 4.0 mm patients over 3.2 kg) is anastomosed in an end-to-side fashion to the artery; this can be done either while cooling or before commencing cardiopulmonary bypass. The clamp is removed, and flow is assessed. If blood does not flow easily out of the open shunt, the anastomosis should be revised. A large hemoclip is placed to temporarily occlude the shunt. An alternative source of pulmonary blood flow is a 5.0-mm RV–PA shunt described initially by Norwood and repopularized by Sano. Some institutions have reported that this technique provides a smoother postoperative course and it has gained wide popularity.[31,32]

On initiation of circulatory arrest, snares are brought down around the brachiocephalic vessels, and a spoon clamp is placed on the descending aorta distal to the ductal insertion site. Cardioplegia is administered in a retrograde fashion through a side port on the arterial cannula. After the patient's blood volume has been drained into the reservoir, all cannulae and PA snares are removed. The ductus arteriosus is

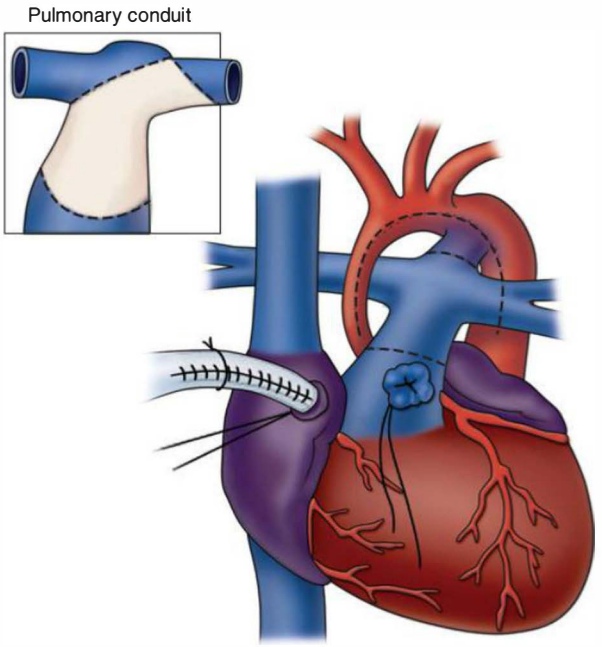



**FIGURE 76-2** Incisions for hypoplastic left heart syndrome first-stage palliation. Cannulation is performed with an arterial cannula in the base of the main pulmonary artery and a single venous cannula through a generous purse string around the right atrial appendage. Subsequent incisions, as described in the text, are indicated by the dotted lines. The patch for aortic augmentation and completion of the aortopulmonary anastomosis is fashioned from a pulmonary homograft (insert). (Reprinted with permission from Gruber P, Spray T, et al. Hypoplastic left heart syndrome. In: Kaiser LK, Kron IL (eds). *Mastery of Cardiothoracic Surgery*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2007:938.)

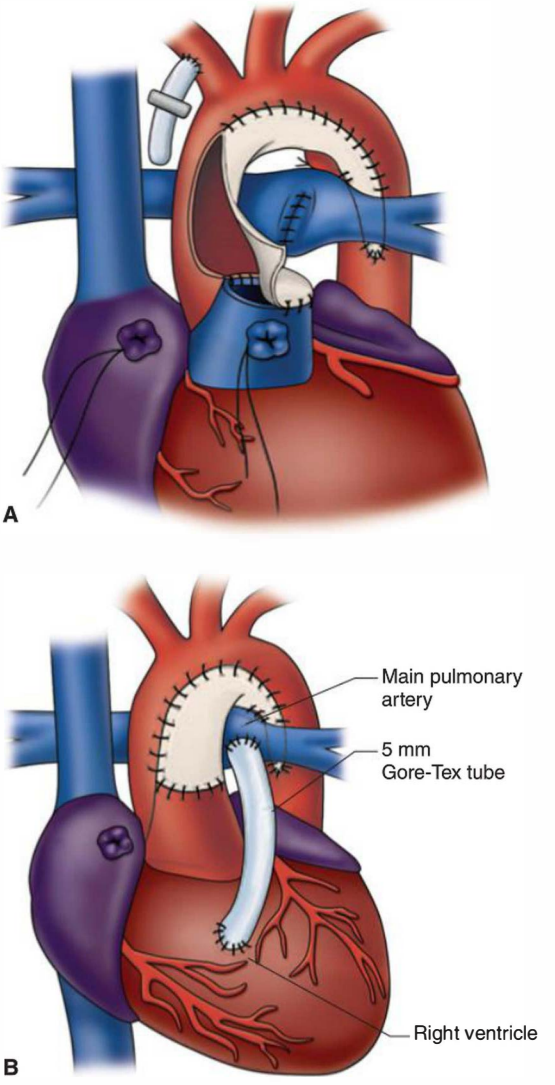



**FIGURE 76-3** Damus–Kaye–Stansel anastomosis (DKS) and aortic arch reconstruction. After complete excision of ductal tissue and an interrupted anastomosis of the medial aspects of the aorta and the main pulmonary artery, the homograft patch is used to augment the hypoplastic aortic arch and complete the DKS. The modified right Blalock–Taussig shunt is completed from the innominate artery to the right pulmonary artery (**A**). An alternative approach (Sano modification, **B**) substitutes a right ventricle–pulmonary artery Gore-Tex conduit for the Blalock–Taussig shunt. (Reprinted with permission from Gruber P, Spray T, et al. Hypoplastic left heart syndrome. In: Kaiser LK, Kron IL (eds). *Mastery of Cardiothoracic Surgery*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2007:938–939.)

ligated on the PA side and divided on the aortic side. The atrial septum is excised completely, working through the atrial purse-string sutures. Though it is seldom necessary, visualization can be improved through a right atriotomy. Next, the main PA is divided close to the branch PAs, and the defect in the distal main PA segment is closed with an oval homograft patch or primarily, in a vertical fashion. At a point beginning immediately adjacent to the divided MPA the diminutive aorta is incised medially and the aortotomy is carried superiorly along the underside of the transverse arch through the ductal insertion site to a point approximately 1 cm distal. Importantly, all redundant ductal tissue is excised and the coarctation shelf is sometimes debrided (alternatively, the segment is excised and the isthmus and the dorsal portion of the proximal descending aorta are reanastomosed). The proximal aortic to proximal PA connection is performed using interrupted fine polypropylene sutures to connect the root of the great vessels. Next, the arch is reconstructed using the homograft patch, carrying this suture line down to complete the Damus–Kaye–Stansel (DKS) anastomosis proximally (Fig. 76-3). The distal Blalock–Taussig (BT) shunt anastomosis is performed to the origin of the right PA, although one can also do this during rewarming after removal of the aortic cross-clamp. The arch is infused with cold saline to assess the geometry and rule out kinking or residual obstruction. The atrium is infused with cold

saline to de-air, and the cannulae are repositioned. CPB is begun, and the patient is warmed to 37°C over 20 min. At this point, it is important to assess prompt and equivalent filling of the coronary distributions, and any perfusion defect should be addressed immediately with revision of the aortopulmonary anastomosis. During warming, obvious bleeding should be controlled.

As noted above, in an increasing number of institutions, the RV–PA shunt (Sano modification) is used as a source of pulmonary blood flow. Numerous modifications have been employed, although the learning curve is not as steep as with the classic Norwood procedure using the right-modified BT (mBT) shunt. These refinements include shunt size and structure (e.g., ringed vs non-ringed), PA and ventricular shunt anastomotic techniques (e.g., patch augmentation, bevel size and suture technique), and shunt location (routed to the right or left side of the aorta). Operatively, the other two principal components (atrial septectomy and arch reconstruction) of stage I palliation are identical. The RV–PA conduit is constructed from a 5.0-mm-ringed Gore-Tex graft. The distal end is either sewn directly to the PA at the distal, divided insertion site of the MPA, or sewn into an oval homograft patch. This patch is then used to augment the PA. The RV is then inspected to determine the site of ventriculotomy. The proper site is usually obvious but may entail insertion of a right-angled clamp through the pulmonary valve to aid identification. The anastomosis of the proximal end of the shunt is performed with the heart arrested. There are a variety of techniques that can be employed for the proximal anastomosis, including various bevels, patch augmentation (as with the distal anastomosis), or insertion of the proximal end of the shunt below the epicardial surface into the ventricular cavity. In all cases, the goal is to prevent the occurrence of RV–PA shunt obstruction requiring intervention that is more common with this technique.

A third staged palliative strategy gaining popularity in many centers for a variety of indications is the hybrid procedure.[6,33] Here, the physiological principles are inviolate (unrestricted systemic blood flow, a reliable and measured source of pulmonary blood flow, and an unrestrictive interatrial communication). However, in contrast to the Norwood procedure, the hybrid technique does not require cardiac arrest in the neonatal period. The following strategy is utilized: First, unrestricted atrial communication is achieved by atrial septostomy usually supported by an intraatrial stent. Second, systemic outflow is achieved by ductal stenting. Third, pulmonary blood flow is controlled by placement of bilateral PA bands. There are cogent arguments for why one might want to either perform or delay the large, definitive operation that entails arch reconstruction. However, there are no existing data to definitively support either strategy. Regardless, the hybrid strategy, with a comprehensive stage II palliation (that includes DKS and arch reconstruction along with all the components of the classic stage II cavopulmonary anastomosis) can be performed safely and provides another alternative in cases where stage I might be deemed high risk. One drawback unique to this procedure is the relatively common occurrence of reverse coarctation that occurs in approximately 25 percent of patients.[34] The distal end of the ductal stent can obstruct the more proximal aorta (retrograde aortic arch obstruction, RAAO) potentially limiting coronary and brachiocephalic blood flow, especially in cases of aortic atresia. A number of temporizing solutions to reverse coarctation have been advocated including reverse stenting of the aortic isthmus through the ductal stent as well as reverse BT or central shunts. Future studies will be required to delineate and customize each palliative approach to a particular patient, as it is unlikely that a single strategy will suit all.[35]

Regardless of surgical modification, the average duration of hospitalization is 7 to 21 days, with the limiting factor often being the establishment of adequate oral intake.

## Stage II Procedure

Two important observations by Norwood and colleagues early in the reconstructive experience prompted the institution of an intermediate stage between the initial palliation and the completion of a total cavopulmonary connection. The first observation was that there was time-related interstage mortality; the second was that the chronic volume load of a systemic-to-pulmonary shunt could create diastolic ventricular dysfunction. Thus, an intermediate stage was initiated as either a bidirectional cavopulmonary anastomosis (Glenn shunt) or a hemi-Fontan procedure. A bidirectional cavopulmonary anastomosis sets the patient up for an extracardiac conduit, whereas a hemi-Fontan procedure sets the patient up for a lateral tunnel completion Fontan. No long-term data prove the superiority of one approach over the other. In general, at approximately 4 to 6 months of age, stage I survivors are catheterized to evaluate both pressures throughout the heart and the anatomy of the PAs. The use of a cavopulmonary anastomosis before 3 months of age is usually associated with increased hypoxia and upper-body venous congestion. The technique for a bidirectional cavopulmonary anastomosis is fairly standard (Fig. 76-4A). The approach is through a reoperative median sternotomy, during which care is taken in regard to the dissection of the neoaorta, which is often adherent to the left side of the sternum and somewhat fragile. The patient is cannulated in a standard fashion with an arterial cannula in the neoaorta, a small-angled venous cannula in the SVC, and a straight cannula in the body of the RA. Although it is possible to perform this procedure without CPB, the authors find it considerably easier to use CPB and believe that the anatomic result is improved. Extracorporeal circulation is begun, and a snare is brought down around the SVC cannula after ligation and division of the azygous vein. The previous shunt is divided and ligated near the innominate artery. A vascular clamp is placed at the SVC–RA junction, and the SVC is divided with great care in not injuring the sinus node. The atrial portion is closed in two layers with fine monofilament sutures. The PA is opened at the superior

portion and inspected carefully. If preoperative catheterization revealed PA stenosis, this is addressed with pulmonary homograft patch augmentation. The SVC is then anastomosed to the superior aspect of the right PA as medially as possible toward the left PA. The snare is removed from the SVC cannula, and one or two RA lines are brought into the mediastinum percutaneously from the right and inserted in the body of the RA. The patient is weaned from CPB, and the SVC cannula is removed. Modified ultrafiltration is performed during which all suture lines are checked for hemostasis. At the completion of modified ultrafiltration, the SVC pressure can be measured directly. In general, these patients can be extubated soon after their return to the intensive care unit (ICU).

An alternative operative approach is the hemi-Fontan procedure, which the authors perform under DHCA. The details of this procedure are summarized in Figure 76-4B. The hemi-Fontan is usually performed under DHCA, using a piece of folded homograft to augment the PAs and create the superior cavopulmonary anastomosis and the RA–PA dam simultaneously. This dam subsequently will be removed for the lateral tunnel, completion Fontan operation.

For patients who have undergone a first-stage hybrid procedure, stage II palliation is considerably more complex. Here the following components must be achieved: removal of the atrial stent and septectomy, completion of the DKS anastomosis, stent removal from the duct and aorta that must be reconstructed, and removal of the PA bands with patch pulmonary arterioplasty, if needed.

## Stage III Procedure

Between ages 2 and 5, usually on the basis of a combination of the patient's weight, growth characteristics, and arterial saturations, the patient is reimaged by echocardiography and, occasionally, with cardiac catheterization or magnetic resonance imaging (MRI). If there are no anatomic issues to be addressed with catheter-based intervention (e.g., distal arch coarctation), the patient is referred for Fontan completion via an extracardiac conduit or a lateral tunnel Fontan. For the extracardiac conduit, DHCA or continuous mild–moderate hypothermic bypass with or without aortic cross-clamping is employed, whereas DHCA is used for the lateral tunnel. The approach is through a reoperative median sternotomy. The following paragraph describes the basic steps of the extracardiac Fontan.

The patient is bicavally cannulated in a standard fashion, and an arterial cannula is placed high in the aortic reconstruction. CPB is begun, and tourniquets are applied around the caval cannulae. A vascular clamp is placed at the IVC-RA junction, and the IVC is divided. The atrial portion is closed partially in two layers with fine monofilament sutures. The conduit (18–22-mm Gore-Tex) is trimmed to the appropriate length to avoid compression of the right pulmonary vein (which typically is shorter than one might expect), and a 4-mm fenestration is punched in the medial aspect near the IVC portion. The IVC-conduit anastomosis is completed with monofilament sutures, followed by a side-to-side anastomosis of the remaining cardiac portion of the IVC opening

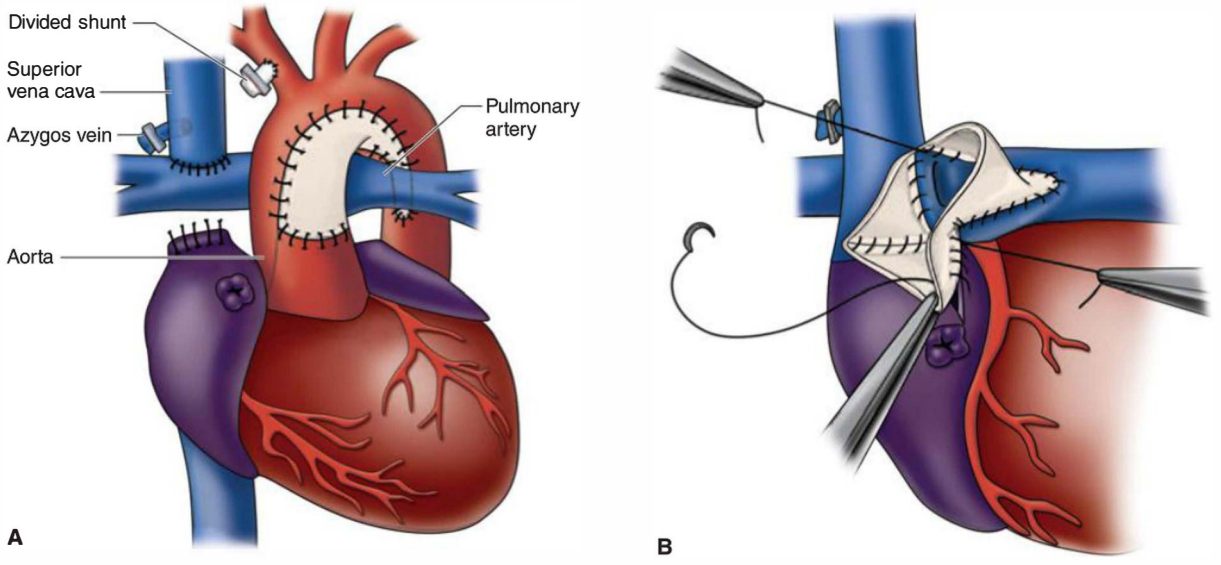



**FIGURE 76-4** Superior cavopulmonary anastomosis. **A.** The bidirectional Glenn replaces the source of obligatory pulmonary blood flow from the Blalock–Taussig shunt to the superior vena cava. **B.** The hemi-Fontan results in precisely the same physiology but uses a single piece of homograft to augment the pulmonary arteries, complete the superior cavopulmonary anastomosis, and create the right atrium–pulmonary artery dam simultaneously. (Reprinted with permission from Gruber P, Spray T, et al. Hypoplastic left heart syndrome. In: Kaiser LK, Kron IL (eds). *Mastery of Cardiothoracic Surgery*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2007:940–941.)

with the conduit, leaving a rim of conduit around the fenestration. Next, the PAs are opened in the inferior portion and inspected directly. If preoperative studies revealed any PA stenosis and the beveled end of the Gore-Tex conduit would not span the area of stenosis, this situation is addressed with pulmonary homograft patch augmentation. The conduit is then anastomosed to the inferior aspect of the PAs, angled slightly medially toward the SVC. The angled nature of the superior portion of the conduit effectively augments the pulmonary confluence from the right to the left PA (Fig. 76-5A). The conduit is infused with saline to de-air, and the patient is weaned from CPB. The SVC cannula is removed, and a period of modified ultrafiltration is begun. All suture lines are checked for hemostasis. At the completion of modified ultrafiltration, the SVC pressure is measured directly with a transthoracic line. An additional monitoring line is placed in the RA. All cannulas are removed, and protamine is administered. In general, these patients can be extubated soon after their return to the ICU.

An alternative operative approach is the lateral-tunnel Fontan, which the authors perform under DHCA. The technical details of this procedure are summarized in Figure 76-5B. The lateral tunnel Fontan is performed under DHCA, using a piece of fenestrated Gore-Tex patch to baffle blood from the IVC to the PAs. The previously constructed PA–RA homograft dam is excised. There are no long-term data suggesting the superiority of one technique over the extracardiac Fontan. Advantages of the extracardiac Fontan include the lack of an atrial suture line and the ability to perform the procedure at mild hypothermia without DHCA or aortic cross-clamping. On the other hand, the lateral tunnel Fontan results in a more reliable fenestration, is faster, and poses no risk of compression to the right superior pulmonary vein.

## OUTCOMES

Despite continued improvement in outcomes, patients with HLHS continue to present a formidable challenge. The authors' group reported the results of the 15-year Children's Hospital of Philadelphia (CHOP) experience with 840 patients undergoing stage I surgery for HLHS between 1984 and 1999. The 1-, 2-, 5-, 10-, and 15-year survivals for the entire cohort were 51, 43, 40, 39, and 39 percent, respectively. A later era of stage I palliation was associated with significantly improved survival, with 3-year survival for patients undergoing stage I reconstruction from 1995 to 1998 of 66 versus 28 percent for those undergoing surgery between 1984 and 1988.[36] More recent studies have shown further improvement and demonstrated that the variability in outcome may be influenced by anatomy. One retrospective study of risk factors for operative and 1-year mortality in 158 patients who underwent the Norwood procedure demonstrated that the diagnosis of HLHS is not a predictor of mortality. HLHS was present in 102 patients, and other forms of functional single ventricle with systemic outflow tract obstruction were observed in the remaining 56. Operative survival for the entire cohort was 77 percent (78 percent for patients with HLHS and 75 percent for patients with other diagnoses). Birth weight, associated cardiac anomalies, total support time, and the need for extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD) support were predictors of operative mortality. Survival to 1 year was 86 percent after successful first-stage palliation,

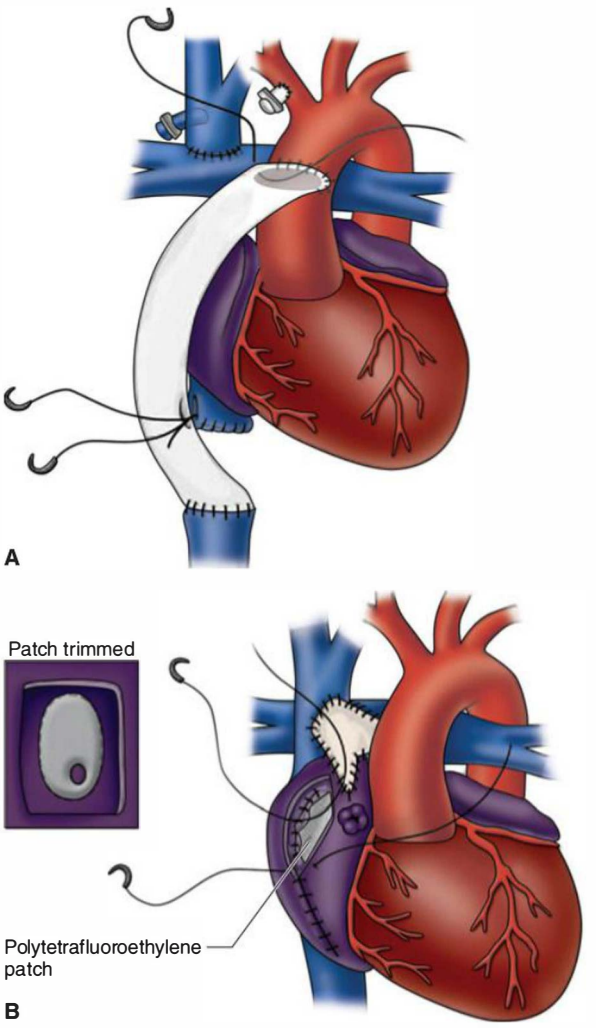



**FIGURE 76-5** Fontan completion. **A.** The extracardiac Fontan uses a Gore-Tex tube graft to channel IVC blood outside the heart to the pulmonary circuit. A 4-mm fenestration is fashioned between the remnant cardiac portion of the IVC and the side of the conduit. **B.** The lateral tunnel Fontan baffles blood from the IVC along the lateral aspect of the atrium inside the heart to the pulmonary circuit. The homograft dam created during the hemi-Fontan is excised to create continuity with the pulmonary arteries. Fenestration patency has proved more reliable in this procedure than in the extracardiac Fontan. (Reprinted with permission from Gruber P, Spray T, et al. Hypoplastic left heart syndrome. In: Kaiser LK, Kron IL (eds). *Mastery of Cardiothoracic Surgery*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2007:943–944.)

although the presence of an extracardiac anomaly, a genetic syndrome, or an additional cardiac defect was predictive of worse survival in the first year of life.[37]

Additional perioperative or operative treatment strategies may improve morbidity and mortality rates. A consecutive series of 115 patients who underwent staged palliation from Milwaukee identified the risk factors for mortality and the impact of new treatment strategy. Between 1996 and 2001, hospital survival was 93 percent compared with 53 percent for the time interval between 1992 and 1996. Survival to stage II palliation was also significantly improved, increasing from 44 to 81 percent. Anti-inflammatory treatment strategies, continuous saturated venous oxygen ($Svo_2$) monitoring, and the use of phenoxybenzamine were factors favoring survival to stage II.[38]

Another approach has been the development of home surveillance programs. One study compared patients discharged before the initiation of home surveillance to those discharged with an infant scale and a pulse oximiter. The parents maintained a daily log of weight and arterial oxygen saturation and were instructed to contact their physicians in case arterial oxygen saturation less than 70 percent, an acute weight loss of more than 30 g/24 hours, or failure to gain at least 20 g during a 3-day period. Interstage mortality was 15.8 percent in the historic group and zero in the monitored group, suggesting that monitoring programs may provide significant benefit in reducing interstage attrition.[39]

As briefly mentioned above, recent reports advocate that an RV–PA conduit (rather than a mBT shunt) may improve the outcome after stage I reconstruction. However, further studies have indicated the need for caution before broad adoption of the RV–PA conduit.[40] The CHOP group compared the outcomes of all neonates who underwent stage I reconstruction between 2002 and 2004 with the use of the RV–PA shunt and mBT shunt. In all, 149 infants underwent a stage I reconstruction for HLHS or its variants. There was no difference in surgical mortality, time to extubation, or length of hospital stay between the two techniques. Although there were no differences in overall mortality, patients with an RV–PA conduit required more conduit-related reinterventions and returned earlier for stage II reconstruction.[41]

The most important individual study to address the value of shunt types is the single ventricle reconstruction (SVR) study. This prospective, randomized, multi-institutional NIH trial that has comprehensively compared the mBT shunt to the RV–PA conduit as sources of pulmonary blood flow in staged palliation for HLHS.[42] The initial report demonstrated that transplantation-free survival at 12 months was higher with the RV–PA conduit than with the mBT shunt (74 vs 64 percent, $P = 0.01$). However, the RV–PA shunt group had more unintended interventions and complications. After 12 months, available data showed nevertheless no significant difference in transplantation-free survival between the two groups. Ongoing a nalysis will determine if the early survival benefit of the RV–PA conduit approach will translate into a long-term survival advantage. For now, the authors feel these should be considered as important experiments in progress. In addition, there may be institution-specific factors for which these multi-institutional studies may not be able to answer.

Patients who have completed staged palliation for HLHS will frequently require reintervention. A study examining these reinterventions during a 6-year period between 1995 and 2001 found that 123 procedures were performed in 71 patients. The median time from Fontan completion to reoperation was 3.6 years, with indication for reintervention including arrhythmia, cyanosis, exercise intolerance, protein-losing enteropathy (PLE), atrioventricular valve (AVV) regurgitation, and other indications. The procedures included pacemaker insertion or revision (48 percent), inclusion of previously excluded hepatic veins (13 percent), revision to a lateral tunnel or extracardiac conduit pathway (11 percent), cardiac transplantation (7 percent), enlargement or creation of baffle fenestration (5 percent), isolated AVV repair or replacement (2 percent), and other procedures (14 percent). There were five early and five late deaths. Hospital mortality was greatest among patients undergoing cardiac transplantation (44 percent), who accounted for 80 percent of the early deaths. Most reinterventions can be performed with minimal morbidity and mortality. However, patients who require cardiac transplantation after a Fontan procedure fare poorly.[43]

For high-risk infants, some have advocated catheter-based hybrid approaches (stage I: ductal stenting and PA banding; stage II: septectomy, arch augmentation, and cavopulmonary anastomosis with or without pulmonary debanding and arterioplasty; stage III: catheter-based Fontan completion). One report of the hybrid stage I procedure in 14 high-risk neonates between 2003 and 2005 demonstrated promising results, with a 78.5-percent hospital survival rate. Eight patients underwent stage II procedures, with two operative deaths. These techniques may be limited in certain anatomic subsets, such as patients with aortic atresia in which preductal retrograde coarctation is a significant problem.[6]

The results from stage III palliation with Fontan circulation also continue to improve. The authors' group reviewed the outcomes of 332 patients: 281 with a lateral tunnel and 51 with an extracardiac Fontan procedure. There was a 93.4 percent hospital survival rate, and by questionnaire, 94.6 percent of guardians described their children's overall health as excellent or good and 5.4 percent reported it as fair or poor. School performance was described as above average in 30.2 percent, average in 39.9 percent, and below average in 29.8 percent. With regard to cardiac functional status, 34.2 percent responded that their children had no limitations to physical activity, 52.5 percent reported a slight limitation, 12.1 percent reported a significant limitation, and 1.2 percent reported a severe limitation. Although these data suggest that acceptable survival outcomes have been observed at intermediate follow-up of the Fontan operation and shed a positive light on the quality of life of this patient population.[44]

In comparing outcomes of extracardiac conduit and lateral tunnel Fontan connections, the results have been conflicting.

The Toronto group reported the results of 60 extracardiac conduit and 47 lateral tunnel total cavopulmonary connections performed between 1994 and 1998. Overall operative mortality was 5.6 percent and did not differ between groups. The lateral tunnel group had a significantly higher incidence of postoperative sinoatrial node dysfunction, supraventricular tachycardia, and need for temporary postoperative pacing. The median duration of ICU stay and the need for ventilatory support were longer in the lateral tunnel group. Holter analysis showed a higher incidence of atrial arrhythmias in the lateral tunnel group.[45]

However, other authors have not found support for one technique over the other. For example, the Charleston group found an incidence of sinus node dysfunction of 21 percent in the lateral tunnel group and 59 percent in the extracardiac group. No permanent pacemakers were placed in the lateral tunnel group, whereas three were placed in the extracardiac group.[46] Another report from the same unit demonstrated identical operative mortality and similar mean Fontan pressures, transpulmonary gradient, and common atrial pressure in the first 24 h after completion of the cavopulmonary connection. Duration of mechanical ventilation, ICU stay, chest tube drainage, and hospital stay did not differ. Again, extracardiac conduit patients had a higher incidence of sinus node dysfunction both in the postoperative period and at hospital discharge.[47] These techniques also appear equivalent in the situation of a failing Fontan, with no hospital deaths, no arrhythmias at hospital discharge, no differences in mean duration of intubation, inotropic support, ICU stay, hospital stay, or episodes of acute postoperative arrhythmias.[48]

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## HYPOPLASTIC LEFT HEART SYNDROME BOARD REVIEW QUESTIONS (CHAPTER 76)

1. Which is the most common form of HLHS?
   A. Aortic stenosis with mitral stenosis
   B. Aortic atresia with mitral stenosis
   C. Aortic atresia with mitral atresia
   D. Aortic stenosis with mitral atresia
   E. Aortic atresia with interrupted aortic arch

2. Which is correct regarding epidemiology of HLHS?
   A. The syndrome is responsible for nearly 50 percent of cardiac deaths during the first week of life.
   B. There is a slight male predominance.
   C. Up to 20 percent will have a chromosomal abnormality.
   D. Williams syndrome is the most common associated syndrome lesion.
   E. Recurrence rate is less than 1 percent for one affected sibling.

3. Which is correct regarding stage I reconstruction for HLHS?
   A. DHCA is required for stage I techniques.
   B. The interatrial septum is carefully fenestrated to calibrate shunting.
   C. The aortotomy is carried under the arch just proximal to the ductus arteriosus.
   D. The proximal end of the Sano shunt is performed with the heart beating.
   E. The hybrid stage I repair is associated with reverse coarctation.

4. Which is correct regarding stage II reconstruction for HLHS?
   A. A Glenn shunt is preferred for patients eventually requiring a lateral tunnel operation.
   B. Use of a cavopulmonary anastomosis before 3 months of age is associated with increased hypoxia.
   C. The hemi-Fontan procedure sets the patient up for an extracardiac conduit.
   D. The SVC is anastomosed as far laterally as possible during the Glenn procedure.
   E. Partial bypass is required for the hemi-Fontan procedure.

5. Which is correct regarding outcomes after surgery for HLHS?
   A. Ten-year survival is 25 percent.
   B. Need for ECMO or VAD support prior to operation does not affect operative mortality.
   C. Home monitoring programs do not significantly reduce interstage attrition.
   D. Use of an RV–PA conduit may improve outcomes after stage I reconstruction.
   E. The most common reintervention is revision of a lateral tunnel or extracardiac conduit.

## ANSWERS

1. **Answer: C.** Aortic atresia with mitral atresia is the most common form, occurring in 40 percent of cases. Aortic stenosis with mitral stenosis and aortic atresia with mitral stenosis both have an incidence of about 30 percent. Aortic stenosis with mitral atresia and aortic atresia with interrupted aortic arch are both rare.

2. **Answer: B.** There is a slight male predominance. HLHS is responsible for nearly 25 percent of cardiac deaths during the first week of life. About 5 percent will have a chromosomal abnormality, with Turner syndrome being the most common. Recurrence rate is 2.2 percent for one affected sibling and 6 percent for two affected siblings.
3. **Answer: E.** The hybrid stage I repair requires stenting of the ductus arteriosus and can result in reverse coarcation by obstruction of the distal aortic arch. DHCA or antegrade cerebral perfusion are both suitable perfusion strategies for stage I techniques. The interatrial septum is completely excised. The aortotomy is carried past the ductus arteriosus to avoid recurrent coarctation. The proximal end of the Sano shunt is performed with the heart arrested.
4. **Answer: B.** Use of a cavopulmonary anastomosis before 3 months of age is associated with increased hypoxia and upper body congestion. A Glenn procedure (bidirectional cavopulmonary shunt) sets the patient up for eventual extracardiac conduit, whereas the hemi-Fontan procedure sets the patient up for eventual lateral tunnel completion Fontan. During the Glenn procedure, the SVC is anastomosed to the right PA as far medially as possible. DHCA is usually required to perform the hemi-Fontan operation.
5. **Answer: D.** The use of an RV–PA conduit may improve outcomes after stage I reconstruction compared to a traditional mBT shunt. Ten-year survival is about 40 percent. Need for ECMO or VAD support is a predictor of operative mortality. Home monitoring programs have provided significant benefit in reducing interstage attrition. The most common reintervention is pacemaker insertion or revision.

77

# Tricuspid Atresia and the Functionally Single Ventricle

*Carin A. van Doorn*
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**KEY CONCEPTS**

- Epidemiology
  - Tricuspid atresia is the most common type of functionally single ventricle. Associated cardiac abnormalities are always present and may lead to obstruction of pulmonary or systemic outflow.
- Morphology and pathophysiology
  - The pulmonary and systemic circulations are in parallel. The degree of hypoxemia depends on pulmonary blood flow, which is determined by the associated cardiac abnormalities and the pulmonary vascular bed, both of which are subject to change over time.
- Diagnosis
  - Echocardiography provides detailed structural and functional information on the heart, particularly in infants. Cardiac catheterization, magnetic resonance imaging, and computed tomography may be necessary to gather additional information.
- Treatment
  - Without surgical treatment the majority of patients will die in infancy, either from severe cyanosis or, less commonly, congestive heart failure. The Fontan circulation is widely accepted as the definitive surgical palliation for patients with tricuspid atresia and other anomalies with functionally single ventricles. There are strict selection criteria for the Fontan operation. In particular, preserved ventricular and valvular function and an adequate pulmonary vascular bed are mandatory. Many patients require preliminary operations in infancy to balance pulmonary and systemic circulations. The surgical technique for the Fontan operation has evolved over time.
- Outcome
  - Operative mortality for suitable Fontan candidates in the current era is approximately 5 percent. Late attrition of the Fontan circulation is a serious clinical problem, and its mechanisms are poorly understood.

## INTRODUCTION

A wide variety of congenital cardiac lesions lack two well-developed ventricles; from a functional standpoint, they are characterized by a single ventricular chamber that supports both systemic and pulmonary circulations. It is well established that the definitive palliation for these univentricular hearts is the Fontan circulation, whereby the pulmonary and systemic blood flow are placed in series with the single ventricle connected to the systemic circulation. To achieve the Fontan state, many patients need preliminary procedures, either to reduce or to augment pulmonary blood flow.

## DEFINITIONS AND ANATOMIC CONSIDERATIONS

A truly morphologic univentricular heart is rare; more often there is an additional rudimentary chamber. The most common type of single ventricle is tricuspid atresia, with an incidence of 1 to 3 percent of all congenital heart lesions. In tricuspid atresia there is no direct communication between the right atrium and the right ventricle, and often a dimple or localized fibrous thickening is found at the expected site of the tricuspid valve. The right atrium is large and an interatrial communication is always present.

The right ventricle is hypoplastic and lacks an inflow portion, but its trabecular and outflow portions may be well developed. Tricuspid atresia is uniformly associated with other cardiac malformations. A ventricular septal defect (VSD) is usually present. The ventriculoarterial connection can be concordant or, less commonly, discordant (transposition of the great arteries); rarely, there is double-outlet right or left ventricle. Infundibular obstruction to pulmonary blood flow is often present, but this can also be observed at the level of the VSD (restrictive VSD) or the pulmonary valve, which may be atretic. In patients with transposition of the great arteries, there may be subaortic stenosis and/or coarctation. The associated cardiac malformations determine the balance between pulmonary and systemic blood flow. Other forms of univentricular hearts include left atrioventricular valve atresia, double-inlet right and left ventricle, hearts with a common atrioventricular valve and only one well-developed ventricle, hearts with heterotaxy syndrome and only one fully developed ventricle, and pulmonary atresia with an intact ventricular septum and hypoplastic right ventricle. In addition, some complex hearts with two well-formed ventricles cannot be septated and become candidates for a single-ventricle strategy as the only viable surgical option. Examples of the latter morphologic group are hearts with major straddling of the atrioventricular valves, or certain forms of double-outlet right ventricle, or transposition of the great arteries with remote VSD. Hypoplastic left heart syndrome, a common form of univentricular heart, is detailed in Chapter 76.

## HISTORICAL HIGHLIGHTS

With the advent of the Blalock–Taussig shunt in 1944,[1] palliation became possible for patients with single-ventricle physiology and cyanosis. Pulmonary artery banding was introduced in 1952 by Muller to alternatively reduce excessive pulmonary blood flow.[2] Following extensive laboratory work, Glenn showed that partial right heart bypass was possible in a patient with tricuspid atresia by anastomosing the superior vena cava (SVC) (or azygos vein) to the divided right pulmonary artery.[3] This procedure evolved to the bidirectional cavopulmonary shunt, in which the SVC is anastomosed end to side to the undivided pulmonary artery, thus shunting blood into both lungs.[4] In 1968, Fontan and Baudet performed the first total right heart bypass operation by establishing an atriopulmonary connection in a patient with tricuspid atresia.[5] The operation was based on the concept that the hypertrophied right atrium could replace the right ventricle as the driving force for the pulmonary circulation. In addition, separating the systemic and pulmonary circulations and placing them in series improved arterial oxygen saturation and reduced volume load on the single ventricle. Over the years, there have been several modifications of the Fontan procedure. It became apparent that the atrial "kick" was not essential to cardiac output, and the atriopulmonary connection has now been largely replaced by the more energy-efficient total cavopulmonary anastomosis.[6] In this palliative configuration, the SVC drains directly into the pulmonary artery and an intra-atrial tunnel or, more recently, an extracardiac conduit[7] is used to baffle the inferior vena cava (IVC) to the pulmonary artery. For patients with subaortic obstruction undergoing the Fontan procedure, Waldman described the concurrent use of a modified Damus–Kaye–Stansel procedure to achieve unobstructed systemic outflow.[8] Staging of Fontan palliation was introduced in an attempt to reduce the operative risk of the Fontan operation. Initial performance of a superior cavopulmonary shunt was followed at a later stage by completion of the total cavopulmonary connection.[9] Another modification in technique was the creation of a fenestration in the Fontan baffle to allow a right-to-left shunt to maintain systemic ventricular filling. This proved to be particularly important in patients with impaired pulmonary blood flow, albeit at the cost of variable degrees of cyanosis. The fenestration can be closed percutaneously.[10] Improved understanding of the Fontan physiology and evolution of the surgical techniques have extended the original indication of the Fontan operation from tricuspid atresia to many other forms of complex univentricular hearts.[11]

## PATHOPHYSIOLOGY

In tricuspid atresia, the systemic venous return crosses the interatrial communication to the left atrium, where it mixes with pulmonary venous blood. As a result, oxygen saturations in the ventricles, aorta, and pulmonary artery are virtually identical (Fig. 77-1). The presence of an unrestrictive atrial septal defect (ASD) is obligatory. Systemic arterial desaturation is always present but is worse when the pulmonary-to-systemic blood flow ratio is low (in case of associated pulmonary stenosis or restrictive VSD). In case of severe hypoxemia, metabolic acidosis will eventually develop. In tricuspid atresia with normally related great vessels, blood reaches the pulmonary artery indirectly through a VSD and hypoplastic right ventricle. Pulmonary blood flow may be unrestricted initially but usually diminishes over time due to restriction of the VSD or the development of infundibular stenosis. In tricuspid atresia with transposition of the great arteries, the left ventricle is connected directly to the pulmonary artery and, unless pulmonary stenosis is present, pulmonary blood flow is high and pulmonary vascular disease may develop. In this anatomic subgroup, the aorta receives blood indirectly via the VSD and the hypoplastic right ventricle. Progressive restriction of the VSD will produce the effect of developing subaortic stenosis. Similar issue may present after pulmonary artery banding. In patients with functionally single ventricles with other morphologic features, the pathophysiology will be determined by the balance between pulmonary and systemic blood flow, the effects of intracardiac mixing and streaming, and the presence of other cardiovascular pathology (such as abnormal pulmonary venous drainage or atrioventricular

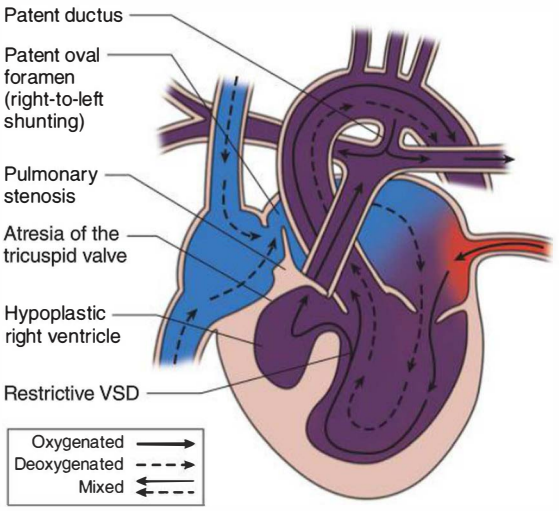



**FIGURE 77-1** Diagram illustrating the pathophysiology of tricuspid atresia. VSD, ventricular septal defect. (Reproduced with permission from Reitz BA, Yuh DD (eds). *Congenital Cardiac Surgery*. New York: McGraw-Hill, 2002:144. With permission.)

valve regurgitation). In most single-ventricle circulations, systemic ventricular dysfunction and failure can develop as the result of cyanosis and/or volume overload.

## NATURAL HISTORY

The natural history of single-ventricle circulations is predominantly related to the degree of pulmonary blood flow and any associated cardiac lesions. There may also be associated noncardiac abnormalities, which will have an independent impact on outcome. Early onset of cyanosis is a predictor of worst survival, leading to death in 90 percent of untreated cyanotic patients with tricuspid atresia in the first year of life.[12] Patients with unobstructed pulmonary blood flow also fare poorly, often dying in infancy from congestive heart failure or early onset of pulmonary vascular disease. This clinical course may be accelerated in the presence of left-sided obstruction, such a subaortic stenosis or coarctation. A small subset of patients has a balanced circulation with unobstructed systemic blood flow and adequate restriction to prevent pulmonary overcirculation. These patients have a more favorable prognosis, with a mean survival of 8 years.[13] Without surgical intervention, only 10 percent of infants will be alive by the age of 10 years.[14]

## CLINICAL PRESENTATION

The clinical features are determined by the degree of pulmonary blood flow and associated cardiac malformations (Fig. 77-2). Most patients with tricuspid atresia present with cyanosis in the first days of life. Some may have a duct-dependent pulmonary circulation and will become rapidly cyanotic as the ductus arteriosus closes after birth. In the majority of patients, cyanosis is progressive and due to increasing infundibular stenosis and/or restriction of the VSD. Hypoxic spells may occur and are characterized by cyanosis, dyspnea, and occasionally syncope. Clubbing may develop in older children. In a minority of patients, however, there is no obstruction to pulmonary blood flow, and these patients present with congestive heart failure from overcirculation. With falling pulmonary vascular resistance, symptoms will grow worse in the first weeks of life. In most univentricular hearts there is mixing of circulations, but streaming may occur, particularly in complex hearts, resulting in differential saturation in the great arteries.

## DIAGNOSTIC MODALITIES

Chest x-ray usually shows signs of low pulmonary blood flow, with reduced pulmonary vascular markings and diminutive hilar shadowing. In cases of high pulmonary blood flow (usually tricuspid atresia with discordant ventriculoarterial connection), there is pulmonary plethora and cardiomegaly. Electrocardiography in most patients will demonstrate left-axis deviation and, frequently, a tall (>2.5 mm) notched p-wave consistent with right atrial enlargement.

Echocardiography provides both detailed anatomic diagnosis and functional assessment. The echocardiogram will usually show a hyperechoic shelf at the expected site of the tricuspid valve, in association with reduced right ventricular dimensions. The following information is essential to allow proper surgical planning: size and course of the pulmonary arteries, relationship of the great vessels, degree of right ventricular outflow tract obstruction, size of the interatrial communication, size and position of the VSD, presence of patent ductus arteriosus, aortic coarctation or other structural cardiovascular abnormalities and, lastly, effectiveness of ventricular function. Particularly in infants (who typically have excellent echocardiographic windows), enough information can usually be acquired to proceed directly to operative intervention. Cardiac catheterization is not routinely performed but remains an important diagnostic adjunct if there is doubt about the size and distribution of the pulmonary arterial supply and a need for direct pressure measurements. In addition, catheter interventions can be performed to supplement or sometimes avert initial surgical intervention. Magnetic resonance imaging and computed tomography are being utilized with increasing frequency to investigate patients with congenital heart disease, allowing for three-dimensional reconstruction of the cardiovascular structures and noninvasive assessment of hemodynamic function. When available, magnetic resonance imaging should serve as the initial screening procedure for preFontan assessment (branch pulmonary artery size and flow, ventricular function, cardiac index, atrioventricular valve function, and residual outflow obstruction) prior to any further diagnostic or interventional catheterization.

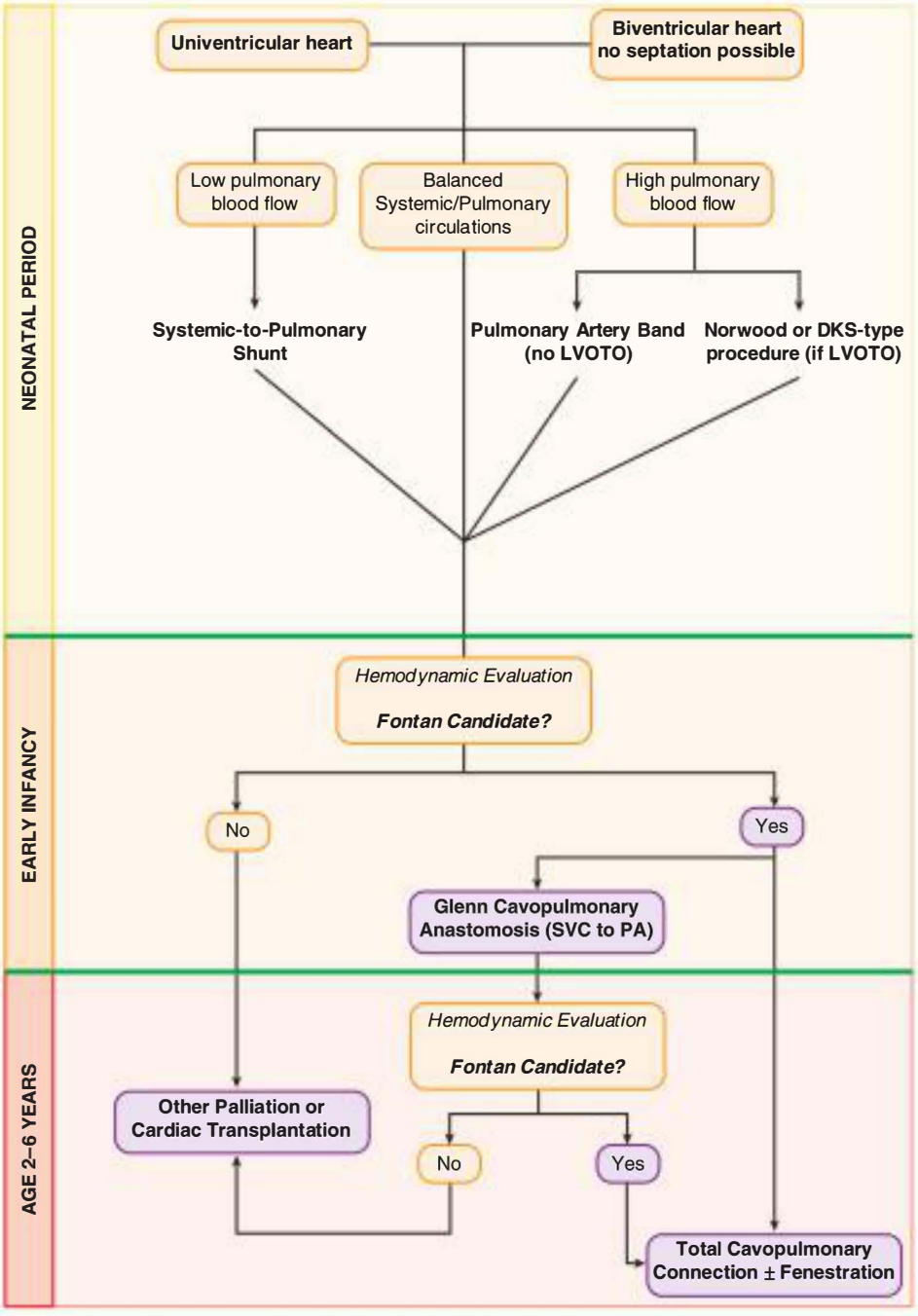



**FIGURE 77-2** Clinical decision-making flowchart for pediatric patients with functionally univentricular hearts.

## SELECTION CRITERIA FOR THE FONTAN PROCEDURE

The initial selection criteria for the procedure, described by Fontan and colleagues for patients with tricuspid atresia, were very strict and known as the "ten commandments" (Table 77-1).[15] With increasing experience, these criteria have been relaxed and, at the same time, the indication for the operation has been extended to many forms of complex single ventricle. However, owing to the unique physiology associated with the Fontan procedure, appropriate patient selection remains of paramount importance.

**TABLE 77-1: The "Ten Commandments" for Selection of Patients with Tricuspid Atresia for the Fontan Procedure**

1. Minimum age 4 years
2. Sinus rhythm
3. Normal caval drainage
4. Right atrium of normal volume
5. Mean pulmonary artery pressure ≤15 mm Hg
6. Pulmonary arterial resistance <4 U/m²
7. Ratio of pulmonary artery diameter to aorta diameter ≥0.75
8. Normal ventricular function (ejection fraction >0.6)
9. Competent left atrioventricular valve
10. No impairing effects of previous shunts

Data from Choussat A, Fontan F, Besse P, et al. Selection criteria for Fontan's procedure. In: Anderson RH, Shinebourne EA (eds). *Paediatric Cardiology.* Edinburgh: Churchill Livingstone, 1978:559–566. With permission.

The minimal age of patients undergoing the Fontan operation has been progressively lowered in an attempt to try to minimize the deleterious effects of long-standing cyanosis and volume overload. The optimal and minimal ages are not known, but successful Fontan operations have been performed in patients as young as 7 months who presented with increasing cyanosis and suitable hemodynamics.[16] It remains to be seen whether a very early Fontan operation has a better long-term outcome, particularly in patients with well-balanced circulations. Preoperative sinus rhythm, normal caval drainage, and normal right atrial volume are not absolute requirements, but unobstructed pulmonary venous drainage is obligatory. The pulmonary vasculature remains an important selection criterion for the Fontan procedure. Mean pulmonary arterial pressure (<15 mm Hg) and pulmonary arteriolar resistance (<4 U/m²) should be low and any pulmonary distortion related to previous shunts should be corrected. Adequate size of the pulmonary arteries is also important. There have been various attempts to standardize pulmonary artery measurements, such as the McGoon ratio[17,*] and the Nakata index,[18,†] but the usefulness of these indices has been questioned, as they do not account for the compliance of the pulmonary vascular bed and they have been established for a biventricular circulation. Adequate ventricular function is also crucial for a successful Fontan procedure. Ventricular impairment, however, is not always an absolute contraindication if it can be related to volume overload in the presence of an aortopulmonary shunt that will be taken down at the time of second-stage palliation. The same is true for mild or moderate atrioventricular valve regurgitation in the setting of a volume-loaded heart. More recently, ventricular hypertrophy has also been recognized as an important risk factor for Fontan failure.[19] Predisposing conditions for ventricular hypertrophy, such as subaortic obstruction or coarctation, should be corrected as soon as possible. In the absence of uniform selection criteria, most centers will use a combination of the above criteria and grade patients as being at low, intermediate, or high risk for the Fontan procedure.

*The McGoon ratio is obtained from the sum of the diameters of the immediately prebranching portions of the left and right pulmonary arteries divided by the diameter of the descending aorta just above the diaphragm.

†The Nakata index is derived from the sum of the diameters of the left and right pulmonary arteries (measured just before the origin of the upper-lobe branches) divided by the body-surface area.

## MEDICAL THERAPY

Medical therapy in the management of the functionally single ventricle is limited to supportive measures. Neonates with severe hypoxemia, in whom pulmonary blood flow is dependent on a patent ductus arteriosus, benefit from prostaglandin $E_1$ infusion until surgical intervention can be undertaken. The same strategy is utilized in patients with associated aortic coarctation and duct-dependent systemic circulation. In those with congestive heart failure, treatment with diuretics is indicated.

## SURGICAL THERAPY

### Preliminary Procedures in Preparation for the Fontan Circulation

The goals of preliminary surgical procedures leading up to the Fontan operation are as follows:

1. Improvement of clinical symptoms
2. Optimization of the pulmonary vascular bed and of ventricular performance
3. Provision of anatomic setup for the Fontan procedure

In the majority of patients with single-ventricle circulation, pulmonary blood flow is restricted; in some it is excessive, and very few have naturally balanced circulations. Within the first year of life, therefore, most patients will require palliative procedures (Chapter 62), either to increase pulmonary blood flow or restrict it. The choice of procedure is guided by the underlying anatomy and pulmonary vascular resistance, both of which are subject to change over time. For augmentation of pulmonary blood flow, a systemic-to-pulmonary artery shunt is usually placed. However, in the subset of patients with transposition of the great arteries with aortic coarctation, a Norwood-type procedure is the best option to relief the obstruction to systemic blood flow at the same time (see Chapter 76). In those with unrestricted pulmonary blood flow, banding of the main pulmonary artery can be used; however, patients with transposition of the great arteries who undergo this procedure need close postoperative monitoring because of the risk for development of subaortic stenosis. In these patients, a Norwood procedure may be considered. It should always be remembered that improper preliminary procedures can result in the loss of Fontan candidacy.

## Bidirectional Cavopulmonary Shunt

The connection from the SVC to the pulmonary artery (Fig. 77-3) can be performed (when no preliminary shunting or PA banding is needed) during the Fontan operation or as the first of two procedures of a staged total cavopulmonary connection. The advantages of a venous-to-pulmonary artery shunt over an arterial shunt are that the venous blood that enters the pulmonary artery is much more desaturated; therefore a higher take up of oxygen per milliliter of blood is possible. In addition, systemic venous blood is diverted to the lungs, thus reducing volume load on the single ventricle. There is no universal agreement on selection criteria for a cavopulmonary shunt, but it is generally accepted that these are less rigorous than those for the Fontan operation. It remains open to discussion whether any additional source of pulmonary blood flow (such as a patent ductus arteriosus, patent right ventricular outflow tract, or systemic-to-pulmonary artery shunt) should be taken down at the time of the cavopulmonary shunt. Any adverse anatomic features for the Fontan circulation should, if possible, be corrected at the time of operation (e.g., atrial septectomy, systemic AV-valve repair). The creation of a cavopulmonary shunt requires complete occlusion of the SVC during the anastomosis. To avoid dangerous levels of upper body venous hypertension, the operation is usually performed on cardiopulmonary bypass. This has the added advantage that the patient's oxygenation will not be compromised if any systemic-to-pulmonary artery shunts are taken down and that, in addition, other cardiac anomalies can be corrected during the operation. An alternative method to achieve decompression of the venous system is the use of a temporary cavoatrial shunt, thus avoiding the deleterious effects of cardiopulmonary bypass. This shunt can be inserted either between the SVC and right atrium or, if pulmonary blood flow is a concern, between the SVC and pulmonary artery. The hemi-Fontan modification of the cavopulmonary shunt involves patch augmentation of the central pulmonary arteries and an anastomosis between the superior cavoatrial junction and the pulmonary artery. This operation has been particularly popular in patients with hypoplastic left heart syndrome in whom, following first-stage Norwood palliation, pulmonary distortion and hypoplasia are common.[20] The hemi-Fontan operation is described in Chapter 76.

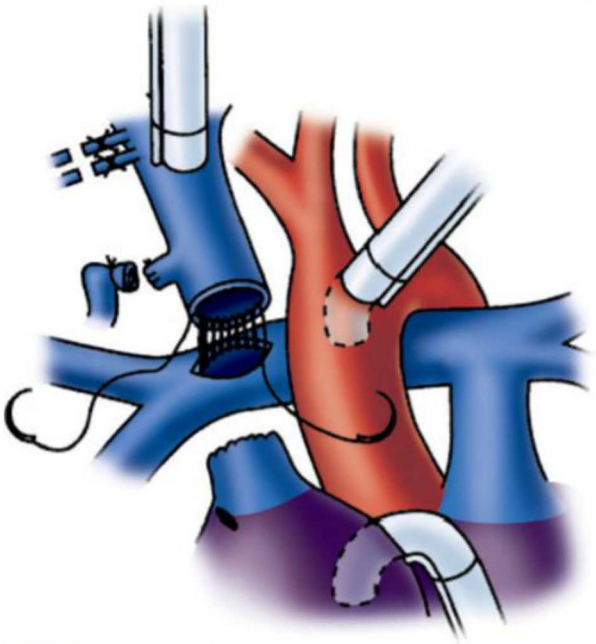


**FIGURE 77-3** Surgical technique for bidirectional cavopulmonary anastomosis (Glenn shunt). The superior vena cava (SVC) and branch pulmonary arteries are fully mobilized. The azygos vein and small venous branches near the innominate vein–SVC junction are ligated to prevent runoff into the inferior vena cava (IVC). If there is IVC interruption with azygos continuation, the azygos vein must be preserved. Cardiopulmonary bypass is instituted with two cannulas draining the right atrium and SVC–innominate vein junction and an aortic return line. The aortopulmonary shunt is subsequently taken down (not seen in the diagram). The SVC is divided and the cardiac end is oversewn. The SVC is anastomosed end to side to the upper margin of the right pulmonary artery. Additional sources of pulmonary blood supply, such as forward flow over a stenosed pulmonary outflow tract or left-sided arterial pulmonary shunt, can be left in place according to institutional preference.

A controversial point in the surgical management plan for the cavopulmonary shunt is whether to leave an additional source of pulmonary blood flow in place (such as an existing aortopulmonary shunt or forward flow over a banded pulmonary artery) with the cavopulmonary shunt. Proponents argue that this adds some pulsatility to pulmonary blood flow, which is more physiologic to the pulmonary vascular bed; those disfavoring this approach are concerned about the increased volume load on the single ventricle.

Complications associated with a cavopulmonary shunt include preferential perfusion of the lower parts of the lung and the formation of pulmonary arteriovenous fistulas.[21] Communications between the (higher pressure) SVC territory and lower body veins, left atrium, and pulmonary veins may also be present, the latter promoting right-to-left shunting and increasing cyanosis.[22] Furthermore, aortopulmonary collateral vessels may impose an increased volume load on the heart. With somatic growth of the child, the relative contribution of SVC return to total venous return decreases, and an additional source of pulmonary blood flow is needed. In suitable patients, total cavopulmonary connection should now be completed. If the patient is not a Fontan candidate, another option may be to add a small arterial shunt to increase net pulmonary blood flow.

## COMPLETION OF TOTAL CAVOPULMONARY CONNECTION

The original atriopulmonary Fontan operation has now largely been replaced by a total cavopulmonary connection. The IVC is connected to the pulmonary artery either

by means of an intra-atrial baffle (Fig. 77-4) or with the use of an extracardiac polytetrafluoroethylene conduit. The latter procedure (Fig. 77-5) can be performed without cross-clamping the aorta and, if a temporary shunt between the IVC and right atrium is used, also without the use of cardiopulmonary bypass. With advances in all aspects of patient management, some centers currently consider fenestration during extracardiac Fontan completion as an exception rather a rule. With this selective approach, there are no survival disadvantages, and the potential risk of hypoxia, systemic embolism, and late instrumentation can be avoided.[23]

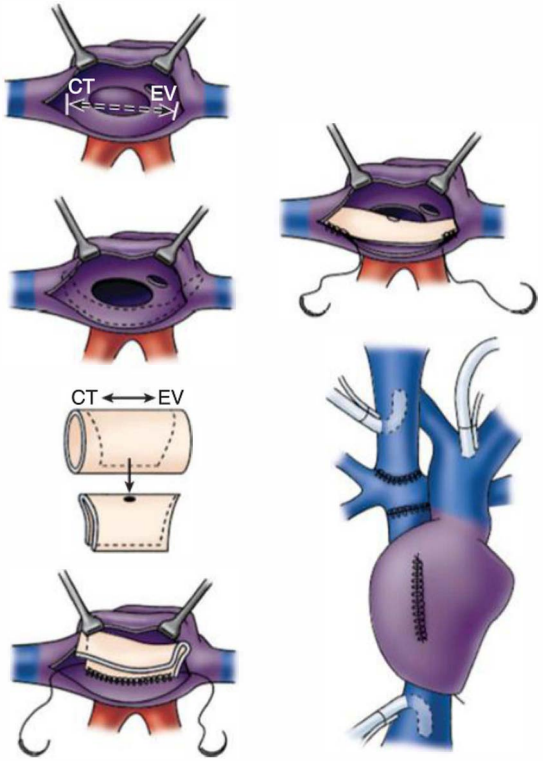



**FIGURE 77-4** Surgical technique for intracardiac Fontan. The beginning of the operation may involve performing a bidirectional cavopulmonary anastomosis (see Fig. 77-3), or this may already be in place. Bicaval venous cannulation and aortic return are utilized to institute cardiopulmonary bypass at moderate hypothermia. The right atrium is opened along the crest of the septum (top left) and the size of the intra-atrial baffle is measured between the eustachian valve (EV) and the crista terminalis (CT). A polytetrafluoroethylene conduit at least 16 mm in diameter is opened longitudinally and, if required, a 4-mm fenestration is performed. The prosthetic baffle is sewn halfway around the junction of the inferior vena cava with the right atrium, along the posterior wall of the atrial septum, crista terminalis, and halfway around the junction with the superior vena cava (SVC) (bottom left and top right). Care is taken to avoid injury to the sinus node. The cardiac end of the transected SVC is anastomosed end to side to the undersurface of the right pulmonary artery (bottom right).

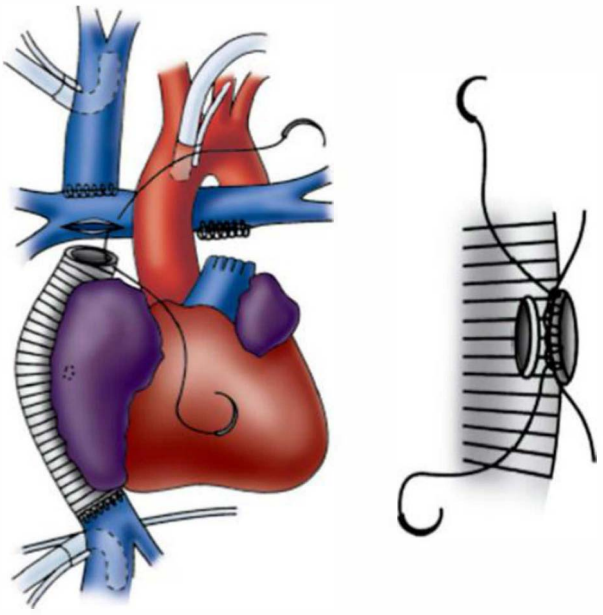


**FIGURE 77-5** Surgical technique for extracardiac Fontan. Cannulation for cardiopulmonary bypass is as described in Figure 77-4. The inferior cavopulmonary junction is transected the cardiac end oversewn. A polytetrafluoroethylene conduit of at least 16 mm in diameter (22-mm diameter in adults) with a tapered end is anastomosed end to end to the transected inferior vena cava. The conduit is gently curved around the right atrium, and the tapered top end of the prosthesis is anastomosed end to side to the underside of the pulmonary arteries. If a fenestration is required, a 4-mm hole is cut in the prosthesis and a larger opening is made in the opposite right atrial wall with side-biting clamps. The two orifices are then anastamosed with a fine suture line away from the fenestration (right).

## OUTCOMES

### Early Mortality and Morbidity

Morbidity and mortality from the various preliminary procedures performed for various structural abnormalities with functionally single ventricle are reported in Chapter 62. The operative mortality for the lateral tunnel Fontan and extracardiac Fontan has decreased steadily and is currently less than 2 percent in best centers.[24–27]

However, in patients with the syndrome of a single ventricle and heterotaxy, mortality is two to three times higher owing to the multiple associated-cardiovascular-abnormalities.[24] When hemodynamic appears stable, early extubation soon after surgery is the preferred pathway. Occasionally, a low cardiac output in the immediate postoperative period can lead to a vicious cycle, resulting in multiple organ failure and death unless early takedown of the IVC connection or fenestration is performed. Such a low-output state can be triggered by various factors, including ventricular dysfunction, subaortic stenosis, raised pulmonary vascular resistance, cardiac arrhythmias, and suboptimal technical procedures.

Investigations should be undertaken promptly. Pleural effusions requiring prolonged chest tube drainage are a common early occurrence after the Fontan operation, and early catheterisation may be indicated.

## LATE RESULTS

The Fontan state is associated with a premature decline in functional status and survival compared with the normal population. In 1990, Fontan and colleagues reported that, even if the operation was performed under perfect conditions, predicted long-term survival was 86, 81, and 73 percent at 5, 10, and 15 years, respectively.[28] In a recent series following patients who had undergone the lateral tunnel Fontan, long-term survival was 93 percent at 5 years and 91 percent at 10 years. For the more recently introduced extracardiac-conduit Fontan, survival up to 8 years is similar.[26] The reasons for the late attrition after the Fontan operation are poorly understood, but chronic elevation of the systemic venous pressure probably plays a major role.

The distended atrium in the atriopulmonary Fontan is prone to dysrhythmias, especially because of the presence of multiple suture lines. The incidence of this has been much reduced in the lateral tunnel Fontan, with reported freedom from supraventricular tachyarrhythmias of 96 and 91 percent at 5 and 10 years, respectively, and freedom from new bradyarrhythmias of 88 and 79 percent at the same follow-up interval.[25] Risk factors for arrhythmias are related to cardiac morphologic features, such as heterotaxy syndrome and atrioventricular valve abnormalities.[25] Five-year follow-up results for the extracardiac Fontan are similar.[29]

Pulmonary arteriovenous fistulas occur both following the cavopulmonary shunt and the Fontan operation. They can produce significant right-to-left shunting with resultant hypoxemia and cyanosis. Their etiology is unclear, but exclusion of the hepatic effluent from the pulmonary circuit may be a factor; resolution has been reported by redirecting hepatic venous blood to the pulmonary arteries.[30]

Thromboembolism occurs both early and late after the Fontan operation and consists of pathway thrombosis as well as pulmonary and/or cerebral emboli. Although the reported incidence ranges from 3 to 16 percent for venous thrombosis[31,32] and from 3 to 19 percent for stroke,[33,34] many events are probably unrecognized. The etiology is likely to be multifactorial and includes suboptimal flow patterns, arrhythmias, thrombogenicity of vascular conduits, hypercoagulable states, and liver dysfunction. Prophylactic long-term anticoagulation remains a contentious issue but is utilized routinely in many centers.

Protein-losing enteropathy (PLE) is a debilitating, poorly understood complication that involves loss of protein from the gastrointestinal tract. It can occur any time after the Fontan operation, with a reported incidence of up to 15 percent and a mortality of 50 percent at 5 years following initial diagnosis.[35,36] Clinical symptoms are related to the degree of nonselective protein loss and include ascites, effusion, peripheral edema, immunodeficiency, and coagulopathy. An elevated fecal $\alpha_1$-antitrypsin level is diagnostic.[37] Medical treatment is often disappointing. High-dose cortico steroids (1–2 mg/kg/day for a minimum of 2–3 weeks)[38] and unfractionated heparin (5000 U/m$^2$/day for several weeks)[39] may benefit some patients. Optimization of the hemodynamics through revision of the Fontan pathways, creation of a fenestration, pacing, or cardiac transplantation has been successful in other cases. In refractory cases, takedown of the Fontan circuit or cardiac transplantation have been performed with regression of PLE.

Pathway problems involving baffle leaks and localized stenoses have been increasingly managed by catheter interventions. In the recently introduced extracardiac conduit Fontan, lack of growth of the tube prosthesis is a potential drawback, but this has not been a problem when conduits between 18 and 20 mm in diameter were used.[29] Conversely, oversizing of the conduit has been complicated by poor hemodynamic performance and conduit thrombosis.[40]

Ventricular dysfunction is common and is multifactorial in origin. The Fontan state itself is associated with a reduction in ventricular preload (suboptimal systemic and pulmonary venous return) as well as an increase in afterload (a single ventricle with the pulmonary and systemic resistance in series), but in the absence of the compensatory increase in contractility seen in normal hearts.[41] Other adverse working conditions include volume overload, subaortic stenosis, atrioventricular valve regurgitation, atrial arrhythmias, and coronary sinus hypertension. In addition, the myocardium in some congenitally malformed hearts may be intrinsically abnormal[42] or the anatomic and structural characteristics may be inadequate to support the systemic circulation. Reduced exercise capacity has been demonstrated in Fontan patients with a morphological right ventricle.[43]

## MANAGEMENT OF THE LATE FAILING FONTAN CIRCULATION

Hemodynamic failure of the Fontan circulation currently occurs predominantly in patients who received an atriopulmonary connection. In those patients who have structural problems of the Fontan pathways or refractory atrial arrhythmias, Fontan conversion to a total cavopulmonary connection with concomitant arrhythmia surgery has been shown to improve exercise tolerance with low incidence of recurrent arrhythmias.[44] Patients with end-stage ventricular failure or other Fontan-related problems refractory to medical treatment should be considered for transplantation. However, pretransplant evaluation of the pulmonary vascular bed in the Fontan circulation is difficult because of the inability to reliably measure pulmonary blood flow, while low pulmonary arterial pressure and transpulmonary gradient may not be predictive of absence of pulmonary vascular disease. The transplant operation itself can be technically challenging because of multiple previous operations and the need for

extensive vascular reconstruction. In small series, operative mortality for transplantation after staged Fontan palliation ranges from 7 to 67 percent,[45,46] with high mortality among potential recipients awaiting a suitable donor allograft.

## FOUR DECADES OF FONTAN PALLIATION

The introduction of Fontan procedure in 1968 has transformed the surgical management of many cardiac lesions with a functionally single ventricle. It was timely that the outcomes and the clinical problems associated with this unique circulation were thoughtfully reviewed in a recent article by deLeval and Deanfield.[11] Many of the achievements and limitations with future challenges were highlighted.

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## TRICUSPID ATRESIA AND THE FUNCTIONALLY SINGLE VENTRICLE BOARD REVIEW QUESTIONS (CHAPTER 77)

1. Which is correct regarding morphology of tricuspid atresia?
   A. The least common type of single ventricle is tricuspid atresia.
   B. The right atrium is small.
   C. The right ventricle is hypoplastic and lacks an outflow portion.
   D. A VSD is usually present.
   E. The ventriculoarterial connection is usually discordant.

2. Which is correct regarding clinical features of tricuspid atresia?
   A. Most patients present with cyanosis in the first day of life.
   B. In most patients, the cyanosis is progressive due to delayed closure of the patent ductus arteriosus.
   C. There is no obstruction to pulmonary blood flow in most patients.
   D. Symptoms may improve as pulmonary vascular resistance increases over the first few months of life.
   E. Electrocardiography demonstrates right-axis deviation and small p-waves.

3. Which is not a criterion for the Fontan procedure?
   A. Age over 1 year
   B. Unobstructed pulmonary venous drainage
   C. Adequately sized pulmonary arteries
   D. Adequate ventricular function
   E. Only mild or moderate atrioventricular valve insufficiency

4. Which is correct regarding bidirectional cavopulmonary shunting?
   A. The venous blood that enters the pulmonary artery is less desaturated.
   B. Systemic venous blood is diverted to the lungs, reducing the volume load on the single ventricle.
   C. Creation of the shunt does not require occlusion of the SVC.
   D. Bidirectional cavopulmonary shunts reduce the formation of pulmonary arteriovenous malformations.
   E. Aortopulmonary collateral vessels reduce the volume load on the heart.

5. Which is true regarding outcomes after Fontan procedure?
   A. Survival at 10 years after the extracardiac Fontan procedure is 80 percent.
   B. Incidence of atrial arrhythmias is reduced after the lateral tunnel procedure.
   C. Arteriovenous malformations are eliminated after Fontan completion.
   D. Thromboembolism rates are less than 10 percent.
   E. Ventricular dysfunction is almost always due to atrioventricular valve regurgitation.

## ANSWERS

1. **Answer: D.** A VSD is usually present in tricuspid atresia. Tricuspid atresia is the most common type of single ventricle. The right atrium is usually large, and the right ventricle is small, lacking an inlet portion. The ventriculoarterial connection is usually concordant.
2. **Answer: A.** Most patients present with cyanosis on the first day of life due to closure of the patent ductus arteriosus. There is obstruction to pulmonary blood flow in the majority of patients. Symptoms may worsen as pulmonary vascular resistance decreases over the first few weeks of life. Electrocardiography demonstrates left-axis deviation and large p-waves consistent with right atrial enlargement.
3. **Answer: A.** Suitable patients under 1 year of age can safely undergo the Fontan operation. Unobstructed pulmonary venous drainage, adequately sized pulmonary arteries, adequate ventricular function, and no more than moderate atrioventricular valve insufficiency are all important criteria for successful Fontan conversion.
4. **Answer: B.** Systemic venous blood is diverted to the lungs, reducing the volume load on the single ventricle. This venous blood is more desaturated than with a systemic–pulmonary shunt. Creation of the shunt requires occlusion of the SVC. Bidirectional cavopulmonary shunts are associated with the formation of pulmonary arteriovenous malformations. Aortopulmonary collateral vessels may increase the volume load on the heart.
5. **Answer: B.** The incidence of atrial arrhythmias is reduced after the lateral tunnel procedure. Survival at 10 years after the extracardiac Fontan procedure is 90 percent. Arteriovenous malformations are not eliminated after Fontan completion. Thromboembolism rates range from 3 to 20 percent. Ventricular dysfunction is multifactorial.

78

# Surgery for Left Ventricular Outflow Tract Obstruction in Children

*Tara Karamlou*
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## KEY CONCEPTS

- Epidemiology
  - Left ventricular outflow tract obstruction (LVOTO) occurs in 2.8 of 10,000 live births, accounting for 3 to 6 percent of congenital heart defects.
- Morphology
  - LVOTO is valvar in 50 percent, subvalvar in 25 percent, and supravalvar in 10 percent of cases. Multilevel obstruction is present in 15 percent of cases.
- Pathophysiology
  - Obstruction at any level causes increased left ventricular systolic pressure and wall stress and consequent left ventricular hypertrophy. Left ventricular hypertrophy produces subendocardial ischemia and diastolic dysfunction. Eventually, myocardial fibrosis occurs with associated left ventricular systolic dysfunction. Low cardiac output, pulmonary edema, and ventricular arrhythmias may occur late and are associated with increased mortality.
- Clinical features:
  - Neonates with critical valvar aortic stenosis (AS) present with low cardiac output and shock, requiring emergency treatment. Other forms of LVOTO are often asymptomatic and may be detected by the presence of a heart murmur or abnormalities on ECG. Chest pain, dyspnea, and palpitations occur with increased activity as the degree of obstruction worsens. Symptoms at rest occur with long-standing LVOTO.
- Diagnosis
  - Diagnostic evaluation is performed in children with a characteristic systolic ejection murmur. Echocardiography allows diagnosis and determines the level(s) of obstruction. The left ventricular outflow tract gradient can be estimated with the use of Doppler flow velocity, and ventricular systolic and diastolic function can be assessed. Diagnostic cardiac catheterization is rarely necessary.
- Treatment
  - Neonates with critical valvar AS and morphology amenable to biventricular repair respond well to percutaneous transcatheter balloon valvotomy. Aortic valve replacement is required in older children. Enlargement of a small annulus may be achieved with the use of Konno aortoventriculoplasty. Options for valve replacement include a bioprosthetic or mechanical prosthesis, or an autograft (Ross procedure), but all have significant disadvantages in the pediatric population. Discrete subaortic membrane is resected via aortotomy, but diffuse tunnel-like narrowing requires a modified Konno procedure. A variety of aortoplasty techniques are available for patients with supravalvar AS.
- Outcomes
  - Excellent outcomes, with operative mortality of less than 5 percent, are achieved in most patients. Reoperation to upsize valves is expected in pediatric patients with somatic growth after aortic valve replacement or for structural valve deterioration. Discrete subaortic membrane recurs in approximately 15 to 20 percent of patients despite successful initial repair, and is dependent on the preoperative gradient.

## INTRODUCTION

Left ventricular outflow tract obstruction (LVOTO) is a relatively common form of congenital heart disease; it occurs in 2.8 per 10,000 births and accounts for 3 to 6 percent of congenital heart defects.[1] The levels of obstruction are classified anatomically as valvar (50 percent), subvalvar (25 percent), and supravalvar (10 percent). Multiple levels of obstruction are present in about 15 percent of cases.[2] LVOTO may be associated with other congenital heart defects, including atrioventricular canal defect, double-outlet right ventricle (RV), and some forms of functionally single ventricle. This chapter focuses on isolated congenital LVOTO in functionally biventricular hearts. Aortic arch interruption and coarctation are specifically discussed in Chapter 79.

## SURGICAL ANATOMY OF THE LEFT VENTRICULAR OUTFLOW TRACT

The left ventricular outflow tract is positioned centrally in the heart in close anatomic relation to other important cardiac structures (Fig. 78-1). Below the level of the aortic valve, the outflow tract is bordered anteriorly and to the left by the infundibular septum. Posteriorly, it is bordered by the anterior leaflet of the mitral valve and by the central fibrous body. The membranous septum is positioned anteriorly and to the right, beneath the junction of the right coronary and noncoronary cusps of the aortic valve. This relationship is surgically important, as the bundle of His courses beneath the membranous septum on the left ventricular aspect and may be injured in the course of resection or suture placement, resulting in complete heart block.

The normal aortic valve consists of three thin leaflets of equal size that are attached to the aortic wall in a semilunar fashion. The so-called aortic annulus, therefore, is not a circular ring but a scalloped coronet.[3] The free edge of each leaflet has an area of central thickening termed the nodulus of Arantius. The leaflet edges coapt in diastole and open freely in systole, creating an unobstructed triangular orifice for the ejection of blood from the left ventricle to the aorta. Leaflets are designated in accordance with the adjacent coronary artery ostia as left, right, and noncoronary cusps.

The proximal ascending aorta constitutes the distal left ventricular outflow tract. Immediately above the ventriculoarterial junction, the aorta enlarges to form the sinuses of Valsalva. These sinuses, like their corresponding valve leaflets, are named for the coronary artery ostia that arise from them. They are important for normal aortic valve function and coronary artery blood flow.[4] The sinotubular junction refers to the normal area of aortic narrowing at the junction between the sinuses of Valsalva and the tubular portion of the ascending aorta. The uppermost point of aortic valve leaflet attachment occurs at the sinotubular junction.

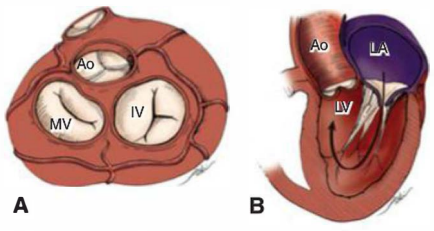



**FIGURE 78-1** Anatomy of the left ventricular outflow tract. **A.** Cranial view. The aortic valve is centrally positioned between the mitral and tricuspid valves. **B.** Schematic left-sided view: The noncoronary aortic cusp is in fibrous continuity with the anterior leaflet of the mitral valve. The bundle of His courses below the membranous septum. Ao, aorta; MV, mitral valve; TV, tricuspid valve; LA, left atrium. (Reproduced with permission from Shizuka N. Aoki.)

## PATHOPHYSIOLOGY OF LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

Regardless of the etiology, obstruction to flow through the left ventricular outflow tract results in increased left ventricular systolic pressure and wall stress. Left ventricular hypertrophy develops as a compensatory mechanism that maintains normal wall stress and stroke volume in accordance with Laplace's law. However, increased ventricular wall mass increases myocardial oxygen demand while limiting diastolic coronary blood flow. Oxygen demand eventually exceeds supply, resulting in myocardial ischemia.[5]

Left ventricular systolic function is initially normal or hyperdynamic in the early stages of obstruction. With progressive left ventricular hypertrophy, decreased wall compliance restricts ventricular filling and produces diastolic dysfunction. A decreased preload reduces stroke volume and cardiac output. Left ventricular end-diastolic and left atrial pressures rise, resulting in left atrial hypertrophy. Patients with long-standing obstruction develop myocardial fibrosis, areas of ischemic injury, and decreased ventricular systolic function. Low cardiac output, pulmonary edema, and ventricular arrhythmias ensue, associated with an increasing risk of sudden death.

Relief of LVOTO ideally is achieved before the development of systolic dysfunction. Early relief of obstruction leads to regression of ventricular hypertrophy and normalization of cardiac function. In the later stages, some components of ventricular dysfunction are likely to be irreversible despite relief of obstruction. Surgical repair in these patients is associated with higher risk and poorer outcomes.

### Valvar Aortic Stenosis

#### PATHOLOGY

Valvar aortic stenosis (AS) in children is most commonly congenital in etiology. The leaflets are thickened and dysplastic, with variable degrees of commissural fusion (Fig. 78-2). The valve is typically bicuspid in morphology but may be

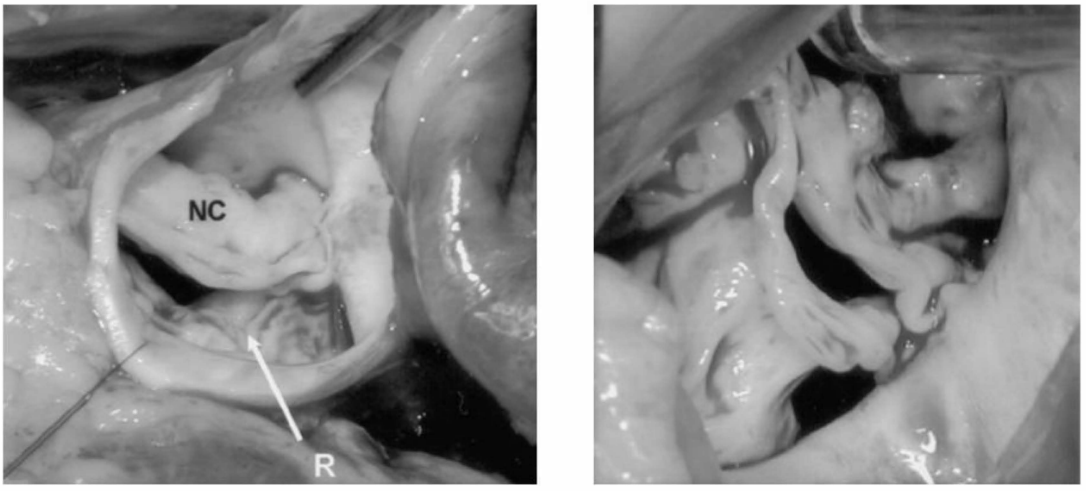



**FIGURE 78-2** Stenotic bicuspid aortic valve. Left: The leaflets are asymmetric, with a larger leaflet resulting from the fusion between the left and right coronary cusps at the raphe (R), poorly coapting against the thickened noncoronary leaflet (NC). Right: Severe calcific stenosis of the bicuspid aortic valve. (Image courtesy of Dr. Duke Cameron, Division of Cardiac Surgery, Johns Hopkins University Hospital.)

tricuspid or even unicuspid. Fusion of the right and left cusps is associated most frequently with stenosis.[6] Obstruction results from decreased leaflet mobility and a reduction in effective orifice size. Small annular size also may be present, further impeding left ventricular ejection.

## CLINICAL PRESENTATION

Neonates with critical AS develop symptoms soon after birth. After closure of the ductus arteriosus, severe outflow obstruction results in pulmonary congestion and poor peripheral perfusion. Dyspnea, tachypnea, and rales are present on pulmonary examination. A systolic ejection murmur may be present, but it may be difficult to hear when cardiac output is reduced severely. The distal extremities have cold, clammy skin with poor capillary refill and thready, rapid pulses. The differential diagnosis includes other causes of shock, including sepsis and other forms of congenital heart disease. Prompt diagnosis and institution of therapy are necessary to prevent rapid deterioration and death.

Older children present less acutely, often with the finding of an asymptomatic heart murmur on routine physical examination. Difficulty feeding in infants and decreased exercise tolerance in older children may be observed as the severity of obstruction increases. Later symptoms include exertional angina, congestive heart failure, and syncope. Physical findings are generally limited to the cardiovascular examination: a harsh systolic ejection murmur at the right upper sternal border radiating to the neck, $S_4$ gallop, and poor upstroke of the carotid pulse. An ejection click may indicate the presence of a bicuspid valve.

## DIAGNOSIS

Chest x-ray is usually nondiagnostic. In neonates with critical stenosis, cardiomegaly and pulmonary congestion are present. Findings in older children generally are limited to moderate left ventricular enlargement, left atrial enlargement, and prominence of the aortic knob.

The electrocardiogram shows left ventricular hypertrophy. Serial findings of increasing QRS voltage and the development of a strain pattern suggest worsening obstruction.

Echocardiography is the principal diagnostic method for the evaluation of LVOTO. Two-dimensional echocardiography allows assessment of aortic valve morphology including leaflet number, degree of thickening, and mobility. Doming of the leaflets is typical (Fig. 78-3). Dimensions of

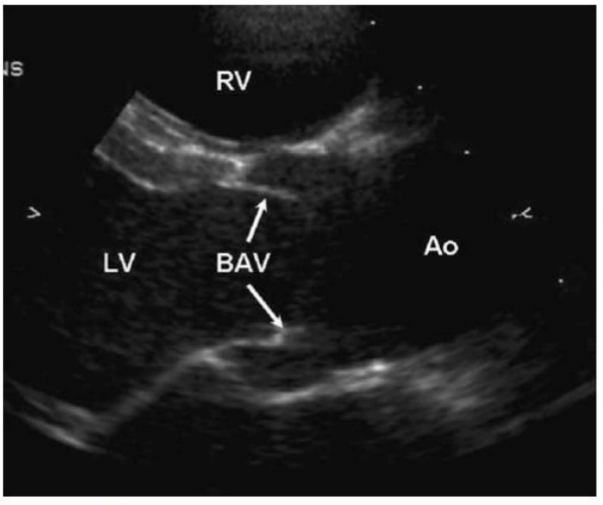



**FIGURE 78-3** Two-dimensional echocardiogram in a patient with congenital aortic stenosis. Long-axis view of bicuspid valve. The leaflets are doming in systole. Ao, aorta; BAV, bicuspid aortic valve; LV, left ventricle; RV, right ventricle. (Image courtesy of Dr. William Ravekes, Division of Pediatric Cardiology, Johns Hopkins Hospital.)

the subvalvar area, annulus, effective valve orifice, and aortic root are measured accurately. Left ventricular cavity size and the presence and severity of left ventricular hypertrophy can be assessed. Indexes of systolic and diastolic function can be calculated. Color Doppler imaging accurately identifies the level of obstruction, allowing a distinction between valvar, subvalvar, and supravalvar stenosis. Doppler measurement of blood flow velocity across the valve provides an estimate of the peak pressure gradient. Progression of disease and timing of intervention, therefore, can be determined in a noninvasive fashion in most cases.

With accurate echocardiographic assessment, cardiac catheterization is rarely required in the diagnostic evaluation of AS. It may be indicated to confirm the diagnosis or assess the severity of obstruction when the clinical and echocardiographic findings are equivocal. Direct simultaneous measurement of left ventricular pressure and aortic pressure is the most accurate method for assessing the outflow tract gradient. However, identification of the precise level of obstruction may not be possible. Elevation of left ventricular end-diastolic pressure indicates impaired diastolic function. Left ventriculography allows assessment of ventricular systolic function and may outline the valve leaflets, providing some assessment of morphology.

## TREATMENT

***Neonatal Critical Aortic Stenosis.*** Critical AS diagnosed in the newborn period constitutes a medical emergency. A neonatal presentation indicates severe outflow obstruction that requires urgent intervention. Initial stabilization includes endotracheal intubation and inotropic support. Prostaglandin infusion will establish or maintain patency of the ductus arteriosus and improve systemic perfusion. Emergency aortic valvotomy previously was the treatment of choice, performed soon after resuscitation. In the current era, percutaneous transcatheter balloon aortic valvotomy has supplanted surgical valvotomy in most centers. The procedure is performed in the catheterization laboratory, with the advantages of rapid relief of obstruction and avoidance of cardiopulmonary bypass and aortic cross-clamping. Risk factors for failure include a small aortic annulus, a bicuspid aortic valve, poor left ventricular function, and limited operator experience.[7,8] Outcomes are generally similar to those for open valvotomy. Hospital mortality for either procedure ranges between 0 and 20 percent.[9,10] Mortality is higher in patients with bicuspid valve morphology. Significant aortic regurgitation is more likely after balloon valvotomy, and is associated with an increased risk of early death.[11] Earlier reports suggested that residual stenosis was more common after surgical valvotomy,[9] though this has not borne out in recent studies. Miyamoto et al. reported an 85 percent freedom from reintervention at 5 years following surgical valvotomy among 34 neonates.[12] Zain and colleagues similarly found that neonates undergoing balloon valvotomy had a higher reintervention rate than those having surgical valvotomy despite a more modest immediate gradient reduction following surgical valvotomy.[13] Regardless of the technique, neonatal aortic valvotomy is considered a palliative procedure for most patients, with 41 percent undergoing reintervention within 10 years.[9,14]

In a small subset of neonates with critical AS and small left ventricular size, it may be difficult to determine whether a biventricular approach with aortic valvotomy/replacement or a single-ventricle approach with the Norwood procedure is more appropriate.[15] Several studies have attempted to identify preoperative predictors for suitability of single ventricle versus biventricular repair in this challenging population.[15] Hammon et al.[16] proposed an angiographically derived 20 mL/m$^2$ threshold for end-diastolic volume for successful biventricular repair. Rhodes and associates[17] identified criteria, including body surface area, indexed aortic root dimension, ratio of left ventricle to heart length, and indexed mitral valve area, as predictors of successful valvotomy. However, the Rhodes score was developed using a small, retrospective group of 65 infants with valvar AS who were pre-selected for biventricular repair. The score has recently been revalidated by Colan et al.,[18] but still has shown poor discrimination when applied to neonates with multiple levels of left heart obstruction or whose primary pathology is other than critical AS. The most robust clinical tool for triaging patients to a single or biventricular pathway, termed the "Critical Aortic Stenosis calculator," was developed by the Congenital Heart Surgeons' Society (CHSS). The calculator was derived from a prospective multi-institutional cohort of 320 patients with critical AS or atresia. Multivariable linear regression analysis identified independent factors associated with survival after biventricular repair versus single ventricle palliation.[19] The derived regression equation requires the following values: age at entry, aortic valve *z*-score, grade of endocardial fibroelastosis, diameter of ascending aorta, presence of moderate or severe tricuspid regurgitation, and *z*-score of left ventricular length. A positive number favors the Norwood approach, a negative number favors biventricular repair, and the magnitude of the number represents the degree of the predicted survival benefit. Individual patient data can be entered and the relative risk of either approach can be estimated by using the website of the Congenital Heart Surgeons Society (www.chssdc.org). An updated analysis of the same CHSS cohort by Hickey et al.[20] allowed refinement of the CHSS prediction algorithm, with substitution of two variables (mid-aortic arch diameter and minimum LVOT diameter) as surrogates for patient age, and the addition of the *z*-score of the mitral valve annulus.

***Neonates with Multilevel Left Ventricular Outflow Tract Obstruction.*** Neonates with multiple levels of LVOTO represent a complex group. Surgical options must be tailored to the particular anatomic considerations (Fig. 78-4). Neonates undergoing single ventricle palliation can be managed with a staged approach, consisting of a Norwood or modified Norwood operation. Hybrid palliation, with implantation of a ductal stent with concomitant bilateral pulmonary arterial (PA) banding, is another recently developed option. This

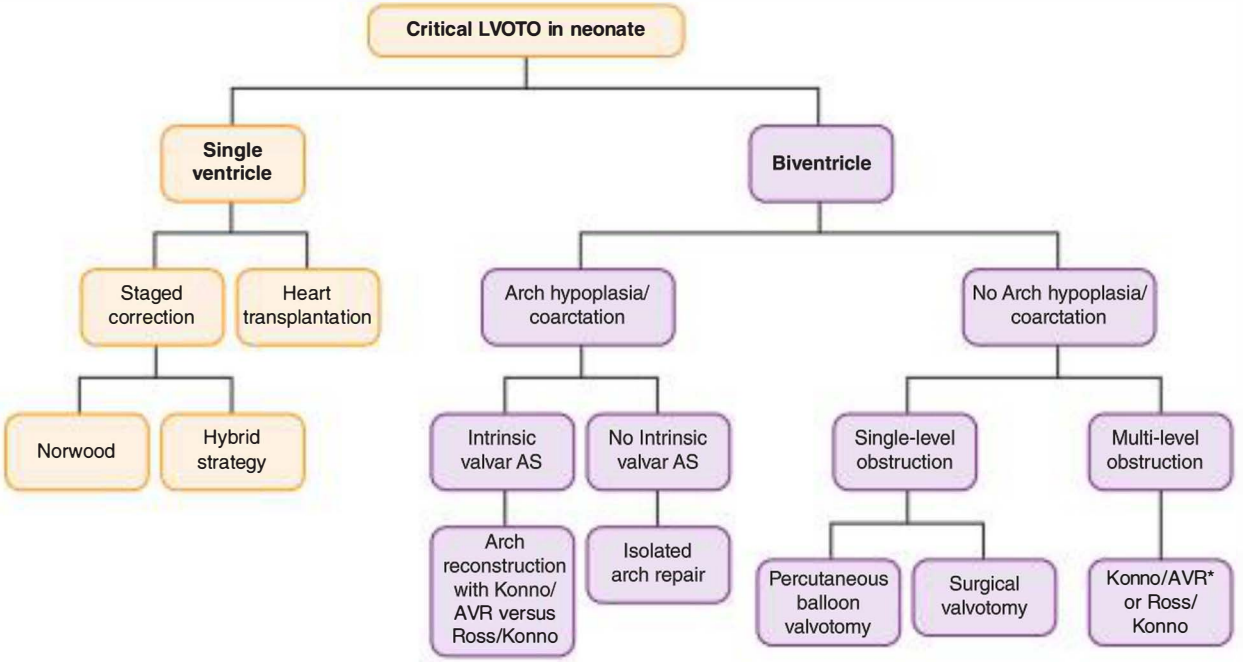



**FIGURE 78-4** Treatment algorithm for neonates and infants with critical left ventricular outflow tract obstruction.

strategy, however, is generally reserved for marginal candidates with contraindications to standard Norwood-type palliation or as a bridge to heart transplantation. Orthotopic heart transplantation is an attractive strategy for infants with severe atrioventricular valve regurgitation, visceral heterotaxy, or poor systemic ventricular function.

Neonates undergoing biventricular repair have several potential options depending upon the associated intracardiac and arch pathology. Infants with combined valvar AS and aortic arch obstruction can be managed with standard patch aortoplasty concomitant with either a neonatal Ross operation or a mechanical aortic valve replacement with an annular enlargement (Konno aortoventriculoplasty). Our institutional preference has been to manage these patients with aortic valve replacement and Konno root augmentation, as results with the neonatal Ross operation have been poor, especially in neonates with associated mitral valve abnormalities.[15,21–23] The presence of a ventricular septal defect adds an additional level of complexity, with options including those discussed above, arch repair with closure of the ventricular septal defect, or a Yasui reconstruction.

***Valvar Aortic Stenosis in Older Children.*** The objectives of surgical treatment of AS are relief of symptoms and reduction of the risk of sudden death. Sudden death is related directly to the severity of obstruction and correlates with the peak systolic gradient, though it is reported to be less than 1 percent.[24] Stenosis is considered severe when the mean echocardiographic gradient is equal to or greater than 40 mm Hg, moderate when it is between 25 and 40 mm Hg, and mild when it is <25 mm Hg.[24] Surgery is indicated in any symptomatic patient regardless of severity, and in asymptomatic patients with severe stenosis. Surgery is not recommended for asymptomatic patients with mild stenosis. There is controversy about the management of asymptomatic patients with moderate stenosis. Surgical management should be considered on an individual basis. The authors generally recommend surgery in patients who demonstrate reduced left ventricular function, a strain pattern on electrocardiography or abnormal exercise testing.

The two options for surgical management of AS are valvotomy and aortic valve replacement. Valve replacement in children poses unique challenges that are not seen in the adult population. The smallest mechanical and bioprosthetic valves available (17-19 mm) are too large for the annular size of smaller children. Even when replacement is feasible, unless an "adult-size" valve is used, somatic growth eventually results in recurrent outflow obstruction because the prosthesis size is fixed. Re-replacement with an appropriately sized valve may be limited by restricted annular growth from the original prosthesis. These limitations may necessitate concomitant annular enlargement, such as in a Konno procedure. Posterior enlargement procedures such as the Nicks or Manougian operations are often insufficient in children.[25,26]

The choices of prosthetic valves for children are more limited than are those for adults. Bioprostheses do not require anticoagulation, but calcific degeneration occurs at an accelerated rate compared with adults, limiting their use in children.[27] Mechanical prostheses maintain their structural integrity and generally have excellent freedom from reintervention or re-replacement,[28–30] but require anticoagulation

with warfarin. Anticoagulation can be achieved safely in children, but issues of compliance, inconsistent diet, and potential for traumatic injury increase the risk of bleeding and thromboembolic complications in this patient population. A recent paper by Alsoufi and colleagues[31] demonstrated that the use of either homograft or bioprosthetic valves in children was associated with an increased risk of valve-related reoperation (82 percent at 15 years) compared to both mechanical valve implantation and the Ross operation. However, long-term survival was excellent (86 percent at 15 years) in patients having homograft or bioprosthetic valve replacement, underscoring the fact that these valve types can be useful in female patients or those in whom anticoagulation cannot be utilized.

Allograft replacement of the aortic root became popular in the early 1990s. Small valves with excellent early hemodynamic performance were readily available, and it was hoped that degeneration would not occur. Subsequent reports, however, demonstrated severe accelerated degeneration that required early reoperation in younger children.[32] Severe calcification and inflammatory reaction of surrounding tissues complicate allograft removal and place adjacent structures, including mitral valve, the bundle of His and the coronary arteries at risk during reoperation.

Pulmonary autografting and reconstruction of the RV outflow tract with an allograft (the Ross procedure) are often the best choice for aortic valve replacement in small children. The autograft has growth potential, does not develop calcific degeneration, and does not require anticoagulation. There are, however, a number of important limitations. The aortic and pulmonary annular sizes must be similar; stretching of the autograft to fit a dilated aortic root will result in neoaortic insufficiency. The operation is technically challenging, requiring longer periods of cardiopulmonary bypass and aortic cross-clamping compared with other, simpler techniques for valve replacement. Allograft reconstruction of the RV outflow tract invariably necessitates eventual reoperation for conduit stenosis from somatic growth or calcific degeneration. Finally, it has been recognized that the pulmonary autograft develops important dilation over time out of proportion to somatic growth, and that this dilation can result in progressive neoaortic insufficiency.[33,34] The propensity for neoaortic dilation was initially thought to be limited to those with aortopathy associated with a bicuspid aortic valve. However, data from Pasquali et al.[33] and others[34] demonstrated that, using serial echocardiographic data, freedom from neoaortic root intervention was 88 percent at 6 years, freedom from moderate neoaortic regurgitation was 60 percent, and freedom from neoaortic root size $Z$-score more than 4 was only 3 percent. Interestingly, several recent papers[33,34] reported that autograft dilation was not associated with the development of neoaortic insufficiency, which was the main reason for reintervention.

In summary, there is no ideal substitute for aortic valve replacement in children with valvar AS. Aortic valvotomy is, whenever feasible, the procedure of choice in this population. Although often not definitive, adequate palliation is usually achieved. Small residual gradients and mild aortic insufficiency are acceptable. Valvotomy can defer the need for valve replacement significantly, allowing for insertion of a larger prosthesis at a later time and reduction of the total number of re-replacements required over a patient's lifetime.

**Aortic Valvotomy.** Surgical aortic valvotomy is usually performed via a median sternotomy. A single right atrial cannula provides venous drainage, and the aortic cannula is placed as distally as possible. Some surgeons advocate closed valvotomy that is performed by passing dilators of increasing size (usually up to 1 mm larger than the preoperative echocardiographic aortic annulus diameter) through the aortic valve; the dilators are introduced through a purse string in the left ventricular apex. This technique can be performed through a left thoracotomy without the need for cardiopulmonary bypass.[35] The authors believe that open valvotomy with direct visualization of the aortic valve allows more precise leaflet separation, resulting in better relief of gradient and a decreased risk of significant aortic insufficiency.

The aorta is clamped, and cardioplegia is delivered via the aortic root. A transverse aortotomy is made just above the sinotubular junction, with care taken to avoid injury to the right coronary artery and the aortic valve leaflets. The valve is inspected carefully. Fused commissures are opened precisely with a scalpel (Fig. 78-5). The incisions are not extended to the aortic wall, since this may result in loss of support and aortic insufficiency. Excessive fibrous tissue, if present, is excised from the leaflets. Fibrous attachments between the base of the leaflets and the aortic wall are divided to maximize leaflet mobility. Despite these steps, the effective orifice may be inadequate, particularly in smaller bicuspid valves. Ilbawi and colleagues[36] described a technique of extended valvotomy for these patients. Circumferential incisions are made above the true commissures and raphes (Fig. 78-6). They reported a low incidence of aortic insufficiency and significantly lower gradients compared with standard

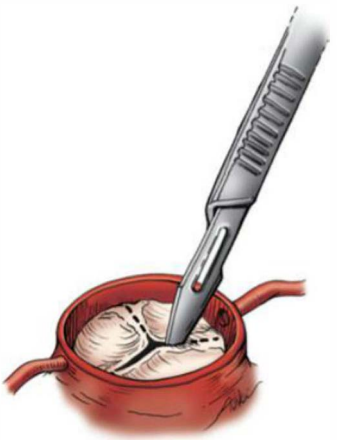


FIGURE 78-5 Open aortic valvotomy. The incision is performed toward the commissural post of the nonfused leaflets. (Reproduced with permission from Shizuka N. Aoki.)

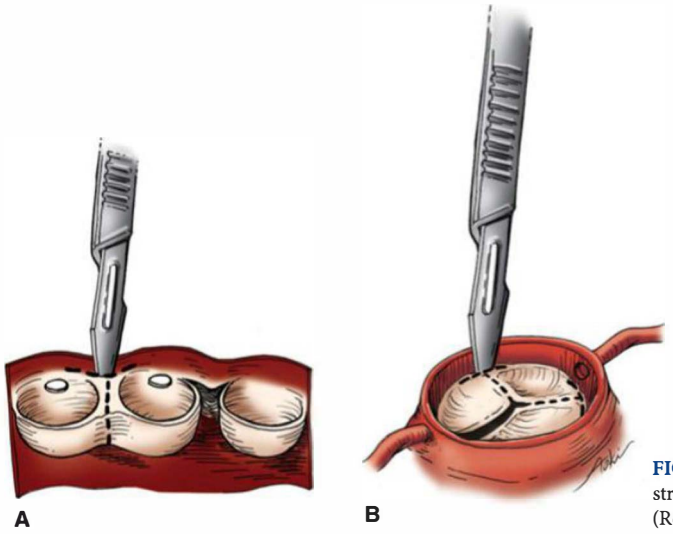



FIGURE 78-6 Extended aortic valvotomy. **A.** Lateral view demonstrating incisions at true commissures and raphe. **B.** Cranial view. (Reproduced with permission from Shizuka N. Aoki.)

valvotomy. The aortotomy is closed precisely to avoid supravalvar narrowing, and the cross-clamp is removed. The patient is weaned from cardiopulmonary bypass with mild inotropic support (dopamine 5 μg/kg/min and milrinone 0.5 μg/kg/min). The adequacy of repair is assessed by transesophageal echocardiography and direct measurement of pressure in the left ventricle and ascending aorta. Modified ultrafiltration is performed before decannulation.

Early mortality in older infants and children undergoing aortic valvotomy is reported currently to be less than 2 percent,[2,7] and late mortality is rare. Reintervention for progressive regurgitation or restenosis may be required, but this generally occurs later than in neonates. Reoperation rate in children over 1 year of age at the time of the initial valvotomy is 2 percent at 10 years but increases thereafter by 3.3 percent per year.[37]

**Aortic Valve Replacement.** Aortic valve replacement is required when valvotomy is not sufficient to reduce the transvalvar gradient adequately, or in patients with greater than mild aortic insufficiency. In larger children with adequate annular size, simple replacement of the valve is performed as it is in adults. Prosthesis selection should be individualized. The authors generally avoid porcine and bovine bioprostheses as well as allograft implantation because of the rapid degeneration and early failure observed in children. The remaining options, therefore, are limited to mechanical prosthesis and pulmonary autograft.

Aortic valve replacement with a mechanical prosthesis is performed via a median sternotomy. A single right atrial or two-stage venous cannula provides venous drainage, and the ascending aorta is cannulated distally. The aorta is clamped, and in the absence of significant aortic insufficiency, cardioplegia is infused in the aortic root. After aortotomy, additional cardioplegia is delivered every 30 min through a retrograde coronary sinus catheter or by direct coronary ostial perfusion. A left ventricular vent is placed through the left atrial appendage or the right superior pulmonary vein.

An oblique aortotomy is made and is extended into the noncoronary sinus of Valsalva. The aortic valve leaflets are excised. Interrupted pledgeted mattress sutures are placed circumferentially around the annulus. In smaller patients, intra-annular placement may be preferable to avoid coronary ostial obstruction by the sewing ring. The sutures are passed through the sewing ring, and the valve is parachuted into place. After the sutures are tied, the prosthetic leaflets are assessed carefully to ensure unhindered mobility. The aortotomy is closed, and the aortic clamp is removed. The patient is weaned from cardiopulmonary bypass on mild inotropic support. Transesophageal echocardiography is used to assess prosthetic function. Modified ultrafiltration is performed before decannulation.

Hospital mortality after mechanical aortic valve replacement in children is less than 5 percent. Early complications include permanent heart block in 3 percent and acute endocarditis in 2 percent of these patients. Late complications relate primarily to anticoagulation. In reports of long-term follow-up, valve thrombosis occurs in up to 2 percent of patients. This sometimes can be managed pharmacologically with thrombolytic agents but frequently requires urgent surgical thrombectomy or valve replacement. Embolic events are reported in 2 percent, and significant bleeding episodes occur at a rate of 0.15 percent/patient year.[38,39] Freedom from reintervention or re-replacement is approximately 86 percent at 20 years, but is increased in younger patients having smaller prostheses.[28–31]

**Ross Procedure.** Ross[40] reported aortic valve replacement with a pulmonary autograft and allograft reconstruction of the RV outflow tract in 1967 (Fig. 78-7). In the absence of significant size discrepancy or connective tissue disease, the Ross procedure is the preferred technique for aortic valve

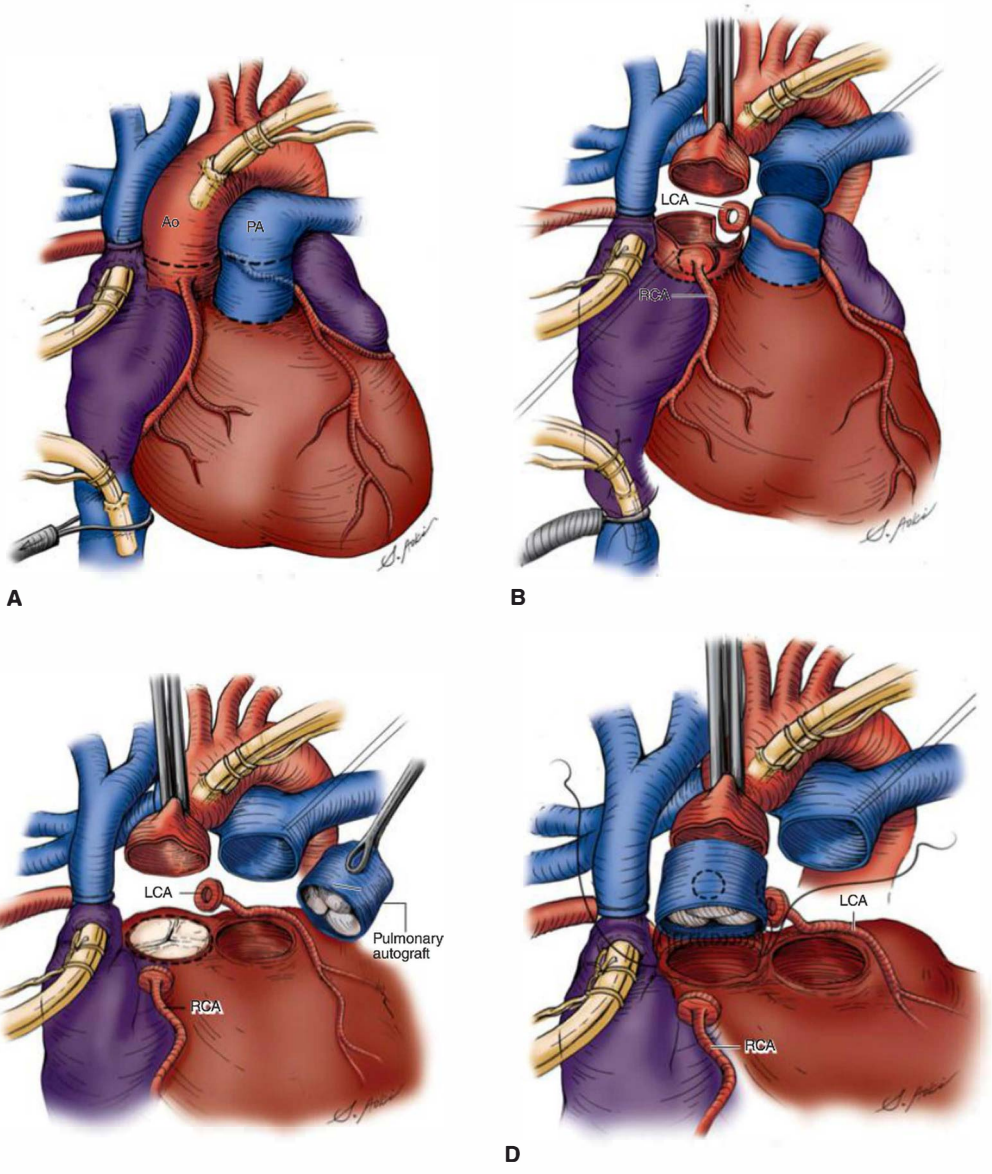
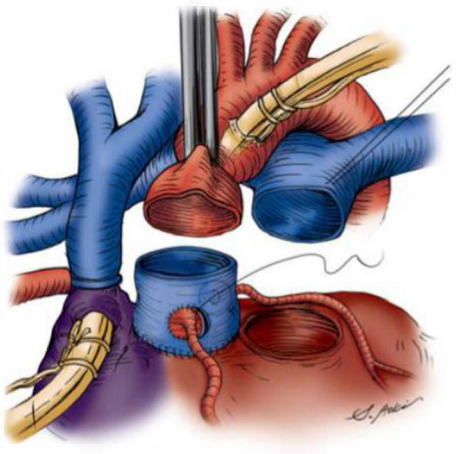



**FIGURE 78-7** Ross procedure. **A.** Dotted lines indicate incisions in the aorta, pulmonary trunk, and right ventricular infundibulum. **B.** The aorta and pulmonary artery are transected, and the coronary buttons are excised from the sinuses of Valsalva. **C.** Removal of the pulmonary autograft. **D.** The proximal anastomosis of the pulmonary autograft is begun posteriorly.

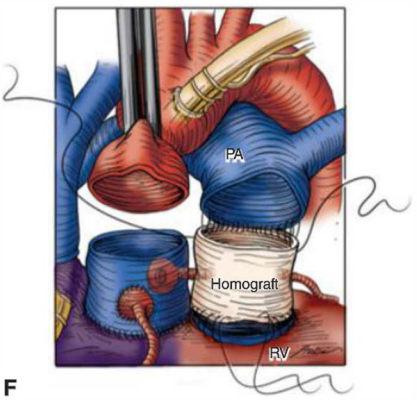
replacement in small children. In larger children, it frequently is preferred over mechanical prosthesis to avoid the need for anticoagulation.

The approach is via a median sternotomy. The venae cavae are cannulated individually, and the ascending aorta is cannulated distally. The aorta is clamped, and in the absence of significant aortic insufficiency, cardioplegia is infused in the aortic root. Cardioplegia may also be delivered in a retrograde fashion with a coronary sinus catheter or by direct coronary ostial perfusion after an aortotomy. Additional cardioplegia is delivered every 30 min during the cross-clamp period. A left ventricular vent is placed through the left atrial appendage or the right superior pulmonary vein.

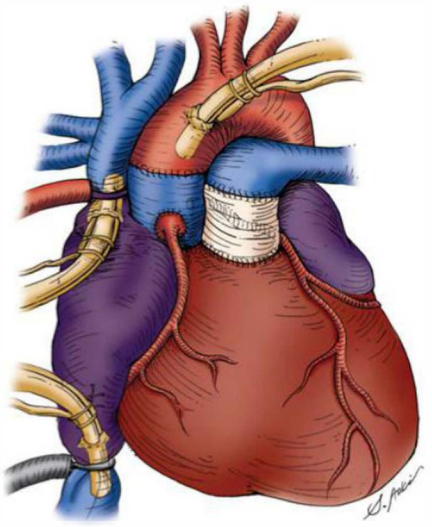
The aorta and the pulmonary trunk are separated, and the pulmonary artery is opened transversely just proximal to the bifurcation. The pulmonary valve is inspected to identify any pathology that would preclude its use as an aortic valve substitute. Transection of the pulmonary trunk is then completed. A right-angle clamp is passed carefully through the leaflets into the RV outflow tract, and a site for proximal transection is identified in the infundibular free wall approximately 5 mm below the level of the valve.



E




F



G

**FIGURE 78-7** (*Continued*) **E.** The proximal autograft anastomosis is completed, and the coronary buttons are sutured to the autograft sinuses of Valsalva. **F.** A homograft restores continuity of the right ventricular outflow tract. **G.** The autograft is anastomosed distally to the ascending aorta. Ao, aorta; LAD, left anterior descending coronary artery; LCA, left coronary artery; PA, pulmonary artery; RCA, right coronary artery; RV, right ventricle. (Reproduced with permission from Shizuka N. Aoki.)

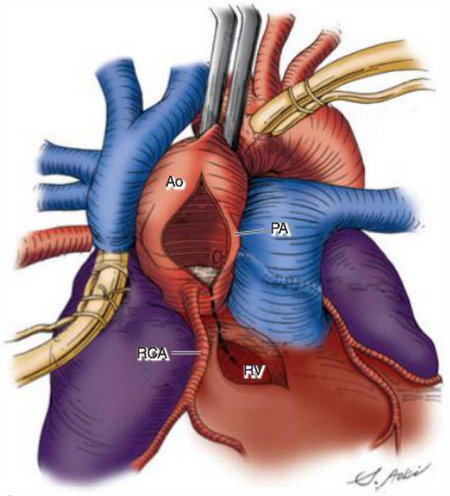
A transverse infundibular incision is made and carried to the infundibular septum at each end. The infundibular septum is scored with a scalpel blade. A plane can be developed between the subconal muscle and the underlying interventricular septum. Dissection in this plane completes the harvest, and the autograft is stored in normal saline solution before implantation. The resulting posterior raw surface is cauterized. In their practice, the authors also apply a thin layer of biological sealant to ensure hemostasis. In dissecting the autograft, care must be taken at the leftward extent of the septal dissection to avoid injury to the first septal perforating branch of the left anterior descending coronary artery. The PA is sized, and an appropriate allograft is thawed and prepared for reconstruction of the RV outflow tract.

The aorta is transected just above the sinotubular junction. The aortic valve leaflets are excised, and the left and right coronary arteries are excised with a generous button of aortic wall. The autograft is oriented by alignment of the commissures. The proximal anastomosis is then constructed. Interrupted simple braided sutures are used for smaller patients, although a continuous technique with polypropylene sutures can be used in larger children and teenagers. The coronary buttons are anastomosed to incisions in the respective autograft sinuses of Valsalva. The distal aortic anastomosis is constructed with a running polypropylene suture. Air is evacuated from the left side of the heart, and the aortic clamp is removed. Continuity between the RV and the PA is restored by interposing the previously thawed allograft in the reperfused, beating heart. The patient is weaned from cardiopulmonary bypass with mild inotropic support. Transesophageal echocardiography is used to assess autograft and allograft function as well as left ventricular wall motion. Modified ultrafiltration is performed before decannulation in children with an operative weight below 20 kg.

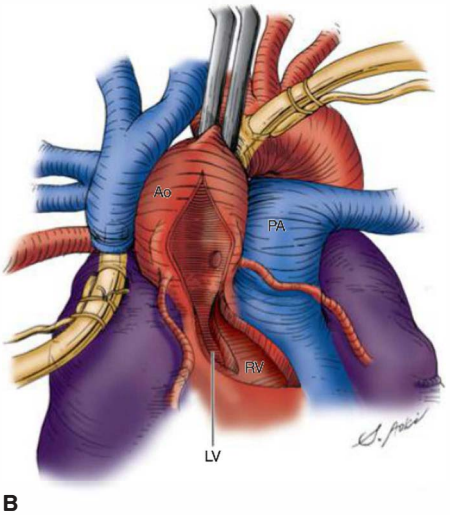
The results of the Ross procedure are reasonable in carefully selected pediatric patients. Early mortality is less than 6 percent, occurring primarily in infants under 5 months of age.[41–44] However, patients with concomitant mitral valve disease or aortic arch hypoplasia, even when judged to have adequate biventricular physiology, fare poorly with the Ross operation. A recent paper by Shinkawa and colleagues from the University of Michigan reported a 36 percent early mortality in this subgroup.[22] Similarly, Hickey and colleagues[23] reported a 31 percent early mortality rate in infants younger than 3 months, and an actuarial 1-year survival less than 50 percent for neonates. Complications occur infrequently and include bleeding, arrhythmia, heart block, and stroke.[43,44] Actuarial survival for all patients is 84 percent at 1 year and 77 percent at 5 years.[22] Aortic root dilatation is common late after the Ross procedure in children as noted above and warrants careful echocardiographic follow-up.[33,34,45,46]

**Konno Aortoventriculoplasty.** Annular enlargement is required in children with small aortic annular size requiring aortic valve replacement. Nicks and colleagues[47] and Manougian and Seybold-Epting[48] described techniques for posterior annular enlargement that have been used successfully in adults. However, the resulting increase in annular size is generally inadequate to allow insertion of even a small prosthetic valve in small children. Konno and coworkers[49] described a technique of anterior enlargement that more effectively increases annular size and relieves coexistent subvalvar stenosis in pediatric patients (Fig. 78-8).

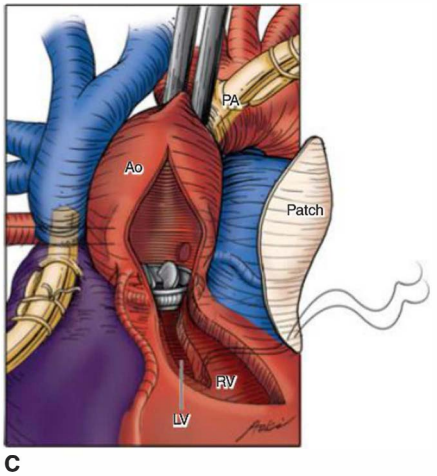
The approach is via a median sternotomy. The venae cavae are cannulated individually, and the ascending aorta is cannulated distally. The aorta is clamped, and in the absence of significant aortic insufficiency, cardioplegia is infused in the aortic root. Additional cardioplegia is delivered every 30 min during the cross-clamp period. A left ventricular vent




A




B




C

**FIGURE 78-8** Konno aortoventriculoplasty. **A.** A longitudinal aortotomy is extended to the right ventricular infundibulum. The incision is to the left of the origin of the right coronary artery. **B.** The aortic leaflets are excised. An incision is made through the annulus and extended into the infundibular septum. **C.** The aortic valve prosthesis is sutured to the annulus posteriorly. The lower portion of a diamond-shaped patch is sutured to the septum, enlarging the annulus and subvalvar area.

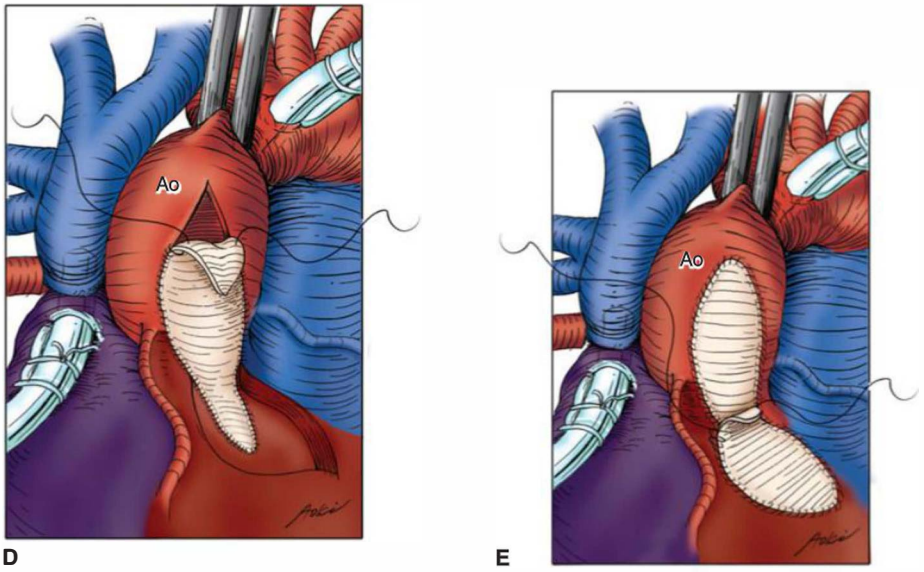



**FIGURE 78-8** (*Continued*) **D.** The prosthetic valve is sutured to the patch anteriorly, and the upper portion of the patch closes the aortotomy. **E.** The right ventriculotomy is closed with a patch of bovine pericardium. Ao, aorta; PA, pulmonary artery; RCA, right coronary artery; LV, left ventricle; RV, right ventricle. (Reproduced with permission from Shizuka N. Aoki.)

is placed through the left atrial appendage or the right superior pulmonary vein.

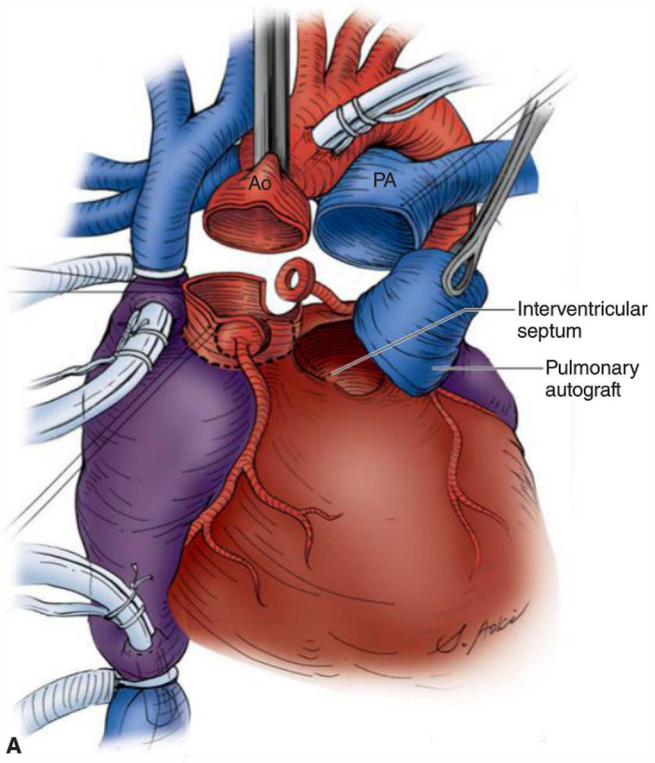
A vertical aortotomy is made and is carried onto the RV outflow tract well to the left of the origin of the right coronary artery. Care is taken to avoid injury to the pulmonary valve. The aortic valve leaflets are excised, allowing visualization of the left and RV aspects of the infundibular septum. An incision is made across the aortic annulus into the infundibular septum. Injury to the conduction tissue is avoided by placing this incision to the left of the papillary muscle of the conus (muscle of Lancisi). A diamond-shaped patch of Dacron is fashioned, and the inferior portion is sutured to the edges of the septal incision with interrupted pledgeted mattress sutures. An appropriately sized prosthetic valve is then inserted as was described for aortic valve replacement. Anteriorly, the valve sutures are passed through the prosthetic patch. The superior portion of the patch is used to close the ascending aorta. The RV free wall is enlarged with a patch of bovine pericardium. Air is evacuated from the left side of the heart, and the aortic clamp is removed. The patient is weaned from cardiopulmonary bypass with mild inotropic support. Transesophageal echocardiography is used to assess prosthetic function, patch leaks, and left ventricular wall motion.

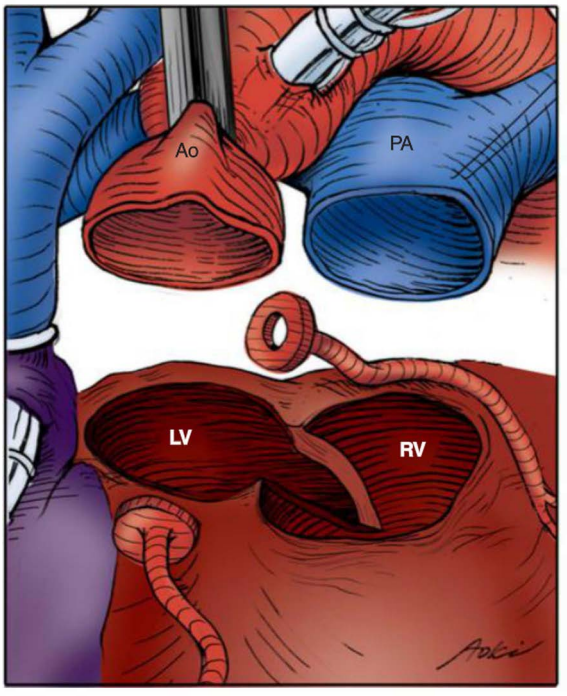
A modification of this technique can be used for annular enlargement in conjunction with the Ross procedure. A Ross–Konno is an ideal procedure in infants or children under 2 years of age, whose size precludes implantation of at least a 21-mm prosthesis or larger. The pulmonary autograft is harvested with a triangular portion of RV free wall that is used as the septal patch (Fig. 78-9).

In light of the complex form of LVOTO seen in pediatric patients who require the Konno or the Ross–Konno procedure, early and late results are quite good. On average, the annulus is enlarged to twice the original size, often allowing insertion of an adult-sized prosthesis (23 or 25 mm) in most patients over 3 years of age.[26,50] Operative mortality for the Konno procedure with prosthetic valve replacement is between 5 and 15 percent. Ten-year actuarial survival is 92 percent.[26] Ten-year freedom from reoperation with a mechanical prosthesis is 80 to 89 percent. The linearized rate of reoperation is approximately 3.9 percent/year, and is increased among patients undergoing a Konno operation to correct aortic valve pathology in conjunction with annular hypoplasia.[25] An important and often underappreciated complication of the Konno procedure (with or without concomitant Ross operation) is pulmonary regurgitation, which occurs at a cumulative incidence of 10 percent at 16 years postoperatively.[25] Operative mortality for the Ross-Konno procedure is 0 to 7 percent even in children under one year of age.[41,51,52] Postoperative complications include bleeding, arrhythmia, heart block, and left ventricular dysfunction. No permanent effects on ventricular function are present at long-term follow-up.[53]

## Subvalvar Aortic Stenosis

Subaortic stenosis in children results from either a discrete fibrous membrane or, less commonly, diffuse, fibromuscular tunnel-like stenosis. The discrete subaortic membrane is probably an acquired lesion that rarely is seen in infants, albeit with "anatomic precursors." An abnormal septal angle



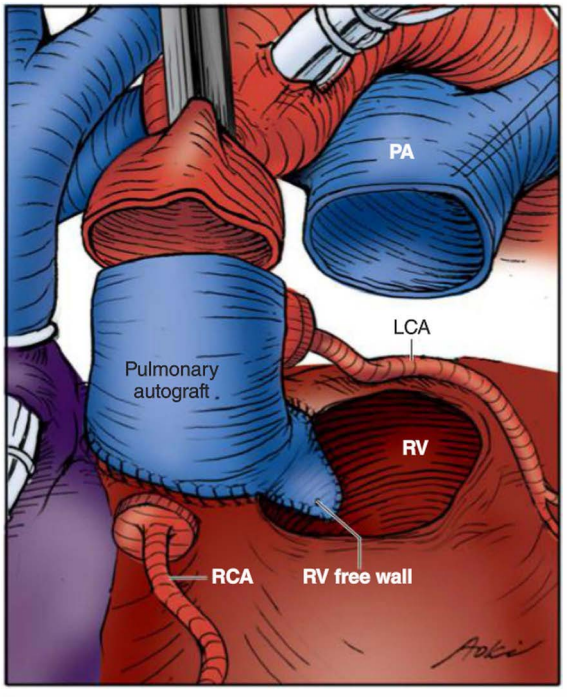




**FIGURE 78-9** Ross–Konno procedure. **A.** The aorta and autograft are prepared as illustrated in Figure 70-6A–C. An incision is made across the aortic annulus and extended into the septum. **B.** The annulus and subvalvar area are enlarged. **C.** The autograft is harvested with a triangular portion of right ventricular free wall that is used for septal closure. LV, left ventricle; RV, right ventricle. (Reproduced with permission from Shizuka N. Aoki.)

between the muscular and conal septum may be an important causative factor, but a definitive etiology has not been established. Turbulence within a small or elongated aortic root causes thickening of the endocardium. A ring of fibrous tissue results that is adherent to the septum anteriorly, extending posteriorly to the right and left fibrous trigones and to the anterior mitral leaflet.[54] Associated subaortic anomalies are present in 31 percent of these patients, including anomalous septal insertion of the mitral valve, accessory mitral valve tissue, anomalous papillary muscles, and anomalous muscular bands.[55] In addition to outflow obstruction, aortic insufficiency develops in more than 50 percent of these patients from turbulence-induced leaflet deformity or direct attachment of the membrane to the aortic leaflets.[56]

Tunnel-like subaortic stenosis is a congenital lesion in which the subaortic region is diffusely hypoplastic. Thickened septal myocardium and endocardial fibrosis contribute to outflow tract obstruction.

## SIGNS AND SYMPTOMS

Patients with discrete subaortic stenosis usually present after infancy when an asymptomatic murmur is detected on physical examination. Early symptoms include feeding intolerance and easy fatigability. Chest pain, syncope, and congestive heart failure may develop with worsening obstruction. A systolic ejection murmur without an ejection click is heard on auscultation. A diastolic decrescendo murmur may be heard at the left lower sternal border when a discrete subaortic membrane is associated with aortic insufficiency. Tunnel-like fibromuscular stenosis often presents in infancy but is otherwise indistinguishable from a discrete membrane on the basis of signs and symptoms.

## DIAGNOSIS

Chest x-ray is usually nondiagnostic. Findings generally are limited to moderate left ventricular enlargement, left atrial enlargement, and prominence of the aortic knob.

The electrocardiogram shows left ventricular hypertrophy. Serial findings of increasing QRS voltage and the development of a strain pattern suggest worsening obstruction.

Two-dimensional echocardiography is the primary imaging modality for diagnosing subaortic stenosis and distinguishing a discrete fibrous membrane from the diffuse fibromuscular type of obstruction. A discrete membrane is usually detected below the aortic valve, extending from the anterior mitral leaflet to the septum (Fig. 78-10). Diffuse fibromuscular stenosis is identified as a long hypoplastic outflow tract (Fig. 78-11). A color Doppler flow study reveals the level of obstruction below the aortic valve leaflets and will detect the presence of aortic insufficiency. Doppler measurement of blood flow velocity in the outflow tract provides an estimate of the peak pressure gradient. Progression of disease and timing of intervention, therefore, can be determined in a noninvasive fashion.

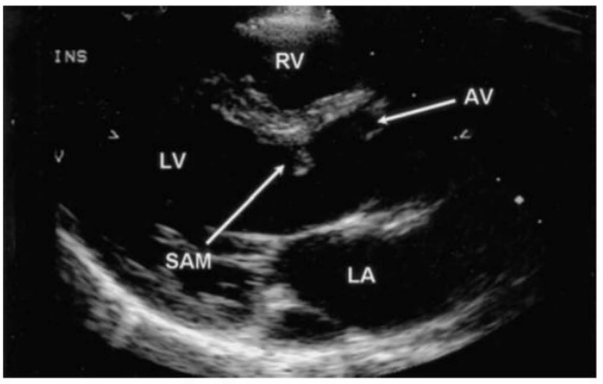



**FIGURE 78-10** Two-dimensional echocardiogram of discrete subaortic membrane. Parasternal long-axis view. AV, aortic valve; LA, left atrium; LV, left ventricle; RV, right ventricle; SAM, subaortic membrane. (Image courtesy of Dr. William Ravekes, Division of Pediatric Cardiology, Johns Hopkins Hospital.)

With accurate echocardiographic assessment, cardiac catheterization is rarely required in the diagnostic evaluation of subaortic stenosis. It may be indicated to assess the severity of obstruction when the clinical and echocardiographic findings are equivocal.

## TREATMENT

***Discrete Fibrous Subaortic Stenosis.*** Surgical excision of a discrete fibrous subaortic membrane is indicated for relief of symptoms, for severe obstruction (mean gradient greater than 30 mm Hg), and when moderate to severe aortic insufficiency is present.[57–59] Asymptomatic patients with mean gradients less than 30 mm Hg and without significant aortic insufficiency do not require surgery but should be followed

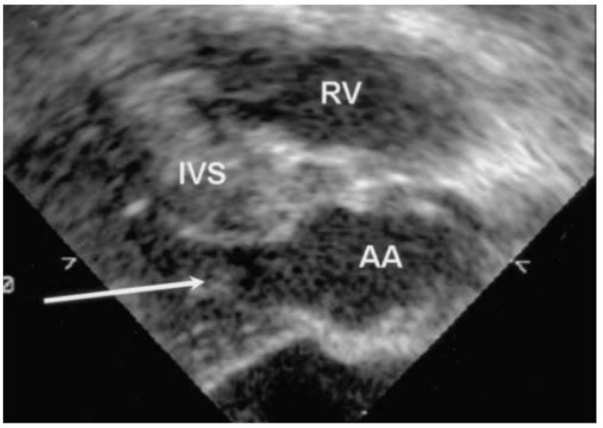



**FIGURE 78-11** Two-dimensional transesophageal echocardiogram of diffuse fibromuscular tunnel-like subaortic stenosis. The arrow points to the subaortic stenotic left ventricular outlet. AA, ascending aorta; IVS, interventricular septum; RV, right ventricle. (Image courtesy of Dr. William Ravekes, Division of Pediatric Cardiology, Johns Hopkins Hospital.)

with serial echocardiograms to detect progression. There is controversy about asymptomatic patients with moderate obstruction and mild aortic insufficiency. Some centers advocate prophylactic excision in all cases, citing the low risk of surgery and the benefit of preventing aortic insufficiency.[60] However, clinically important progression is not universal, and factors determining at-risk substrates are debated.[57] Furthermore, the efficacy of early surgery is controversial because of the variable outcomes in patients undergoing early surgical intervention coupled with a high postoperative prevalence of both recurrent stenosis and aortic regurgitation even after successful relief of subaortic obstruction.[61] Patients with a mean echocardiographic gradient greater than 30 mm Hg, close proximity of the membrane to the aortic valve, and membrane extension to the mitral valve are at higher risk for progressive obstruction and should undergo surgical repair.[62] Older age and a gradient above 30 mm Hg are independent risk factors for progressive aortic insufficiency and are indications for repair.[57,63]

The surgical approach is via a median sternotomy. A single right atrial or a two-stage venous cannula provides venous drainage, and the ascending aorta is cannulated distally. The aorta is clamped, and in the absence of significant aortic insufficiency, cardioplegia is infused in the aortic root. An oblique aortotomy is made and is extended into the noncoronary sinus of Valsalva. The aortic valve leaflets are gently retracted, allowing visualization of the membrane in the left ventricular outflow tract.

The membrane is grasped anteriorly with a skin hook or a traction suture. A radial incision is made into the membrane, initiated just to the left side of an imaginary line descending from the right coronary ostium, extending just into the underlying septal myocardium. The membrane is then excised circumferentially in a counterclockwise direction by blunt dissection. Care is taken to avoid injury to the anterior leaflet of the mitral valve and the aortic valve leaflets. Resection of additional septal muscle is performed to ensure complete excision of the membrane. Yacoub and colleagues[54] advocate the additional resection of fibrous tissue in the left and right fibrous trigones.

The aortotomy is closed, and the aortic clamp is removed. The patient is weaned from cardiopulmonary bypass. Transesophageal echocardiography is used to assess relief of obstruction and aortic insufficiency. Mortality after resection of discrete subaortic membrane approaches zero in most series. Permanent heart block and iatrogenic ventricular septal defect occur in fewer than 5 percent of these patients. Reoperation for recurrent obstruction is required in 15 to 20 percent of patients at 5 years.[60,64,65] Multiple studies have suggested that the risk of recurrent obstruction is increased in patients with higher LVOT gradients following initial resection, thus advocating for aggressive pursuit of any residual LVOT gradient documented by intraoperative echocardiographic or direct pressure measurements.[57,60] Aortic insufficiency progresses in 25 percent of patients at 10-year follow-up, and is more likely in patients with a higher mean postoperative echocardiographic gradient and in patients whose preoperative mean echocoardiographic gradient exceeded 30 mm Hg.

The indications for excision of recurrent discrete subaortic stenosis are the same as those for the initial operation. Re-resection with more aggressive septal myectomy is the authors' procedure of choice. In the case of a second recurrence, a modified Konno procedure is performed as described below for the treatment of tunnel-like stenosis.

***Diffuse Fibromuscular Subaortic Stenosis.*** Indications for surgery in patients with tunnel-like subaortic stenosis are the same as those for patients with a discrete subaortic membrane, but relief of the obstruction is technically more challenging. Furthermore, results following surgical treatment are less favorable in this subgroup of patients compared to those obtained following resection of discrete subvalvar stenosis.[66] Resection of fibromuscular tissue from the septum may be possible, but this is often inadequate because of the long circumferential narrowing of the outflow tract. Conal enlargement with a modified Konno procedure is the preferred approach in these patients (Fig. 78-12).[67]

The modified Konno procedure is performed via a median sternotomy incision. The venae cavae are cannulated individually, and the ascending aorta is cannulated distally. The aorta is clamped and cardioplegia is infused in the aortic root. A transverse aortotomy is made just above the sinotubular junction. The subaortic area is inspected through the retracted aortic valve leaflets. A transverse incision is made in the RV infundibulum, allowing visualization of the infundibular septum. A right-angle clamp is passed through the aortic annulus, and a safe site for septal incision is identified. A full-thickness longitudinal septal incision is made through the right ventriculotomy, and subaortic fibromuscular tissue is resected. The resulting ventricular septal defect is closed with a Dacron or Gore-Tex patch. The right ventriculotomy is closed with a bovine pericardial patch, and the patient is weaned from cardiopulmonary bypass. Early mortality was 0 in several large series of patients who underwent a modified Konno procedure. Excellent relief of obstruction is obtained, with no permanent heart block and no hemodynamically significant residual ventricular septal defects. More long-term follow-up is required, but freedom from reoperation at 3 years has been found to be 95 to 100 percent.[68,69]

Placement of a left ventricular apicoaortic valved conduit has been described for patients with severe outflow tract obstruction considered not amenable to conventional repair.[70] The authors believe that nearly all patients can be treated more definitively with resection and a modified Konno procedure.

## Supravalvar Aortic Stenosis

Supravalvar AS is the least common form of LVOTO. The underlying biochemical mechanism is abnormal elastin synthesis that is related to mutations in the chromosome region 7q11.23. This may occur in association with Williams

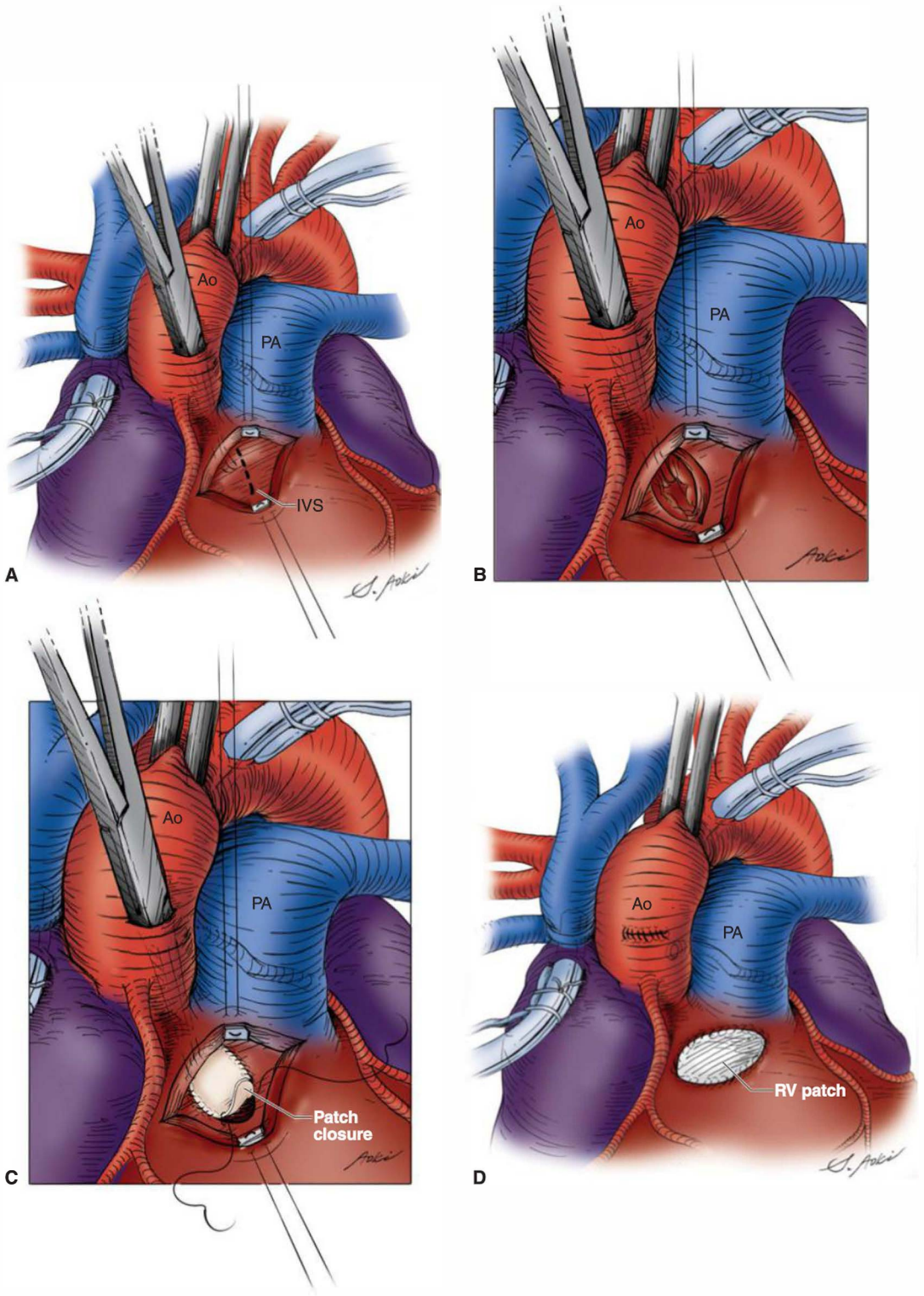



**FIGURE 78-12** Modified Konno procedure. **A.** Transverse incisions are made in the aorta and right ventricular infundibulum. A right-angle clamp is passed through the aortic valve leaflets to identify the site of septal incision. **B.** The septum is incised longitudinally, and fibromuscular tissue is resected. **C.** The ventricular septal defect is closed with a synthetic patch. **D.** The right ventricular incision is closed with a bovine pericardial patch. Ao, aorta; IVS, interventricular septum; PA, pulmonary artery; RV, right ventricle. (Reproduced with permission from Shizuka N. Aoki.)

syndrome, as an autosomal dominant familial trait, or as a sporadic finding.[71]

The pathologic lesion in supravalvar stenosis is a thickening of the aortic wall that results from collagen deposition and smooth muscle hypertrophy in the media as well as hyperplasia and fibrosis of the intima.[72] The narrowing is localized to the sinotubular junction in 85 percent of cases, with either an hourglass or a discrete membranous morphology. Diffuse hypoplasia is present in 15 percent of cases and involves the entire ascending aorta, occasionally extending to the transverse arch and the descending aorta.[73]

Although the site of stenosis may be localized, it is important to recognize that the pathologic process involves the entire aortic root.[74,75] Distortion of the aortic valve and sinuses of Valsalva may occur, including leaflet adherence to the stenotic ridge at the sinotubular junction. Concomitant valvar or subvalvar stenosis is present in 20 to 40 percent of these patients.[73,76,77] Central and peripheral PA stenosis may also occur in association with supravalvar AS.

Coronary ostial stenosis, most commonly involving the left coronary artery, occurs in 25 percent of these patients.[49] Three mechanisms have been identified: (1) thickening of the ostial wall may occur as part of the generalized aortopathy, (2) adherence of the aortic valve cusp to the sinotubular junction may isolate the ostium from the lumen of the aorta, and (3) diffuse narrowing of the left main coronary artery may represent a form of premature atherosclerosis that results from the abnormally high sinus of Valsalva pressures.[78] Ischemic lesions are found in 80 percent of autopsy specimens.[79]

## SIGNS AND SYMPTOMS

Patients with supravalvar AS typically present in the first year of life, although cardiovascular findings are present in less than one-third of these newborns.[80] Symptoms include feeding or exercise intolerance, angina, and syncope. About 10 percent of patients are asymptomatic.[76]

Patients with Williams syndrome may be identified by the presence of dysmorphic "elfin" facies, mental retardation, poor growth, urogenital anomalies, and hypercalcemia. Cardiovascular findings include a systolic ejection murmur with radiation to the neck and poor carotid pulse upstroke.

## DIAGNOSIS

As with other causes of LVOTO, chest x-ray findings are nonspecific. Mild-to-moderate left ventricular and left atrial enlargement may be present.

The electrocardiogram shows left ventricular hypertrophy. ST-segment and T-wave abnormalities consistent with ischemia may be seen in patients with coronary artery involvement. Two-dimensional echocardiography is the usual method of diagnosis in patients with supravalvar AS. Decreased aortic caliber, increased wall thickness, and abnormal leaflet mobility are identified. Localized stenosis can be distinguished from the more diffuse pattern, and the extent of distal involvement can be assessed. Coronary ostial involvement as well as concomitant subaortic stenosis can also be detected. In contrast to valvar and subvalvar stenosis, echocardiographic measurement of peak gradients in supravalvar stenosis correlates poorly with catheter-measured gradients. Echocardiography is, therefore, less helpful in assessing the severity of obstruction and the timing of surgical intervention.[81]

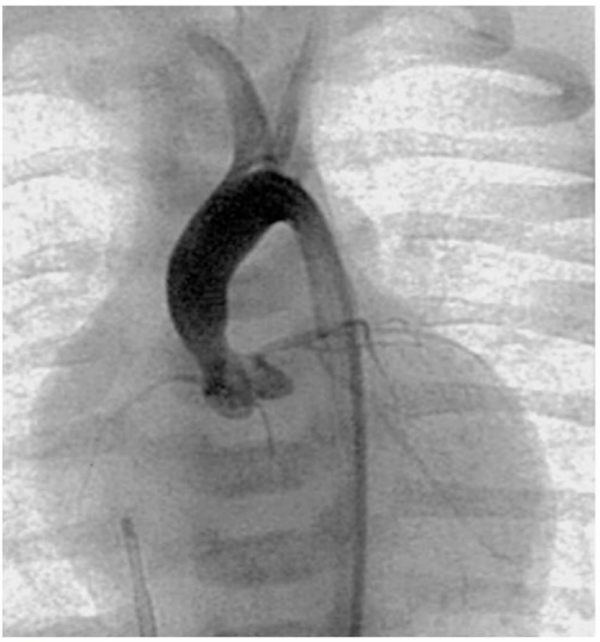


**FIGURE 78-13** Aortogram of supravalvar aortic stenosis. The typical hourglass appearance of the ascending aorta is demonstrated. (Courtesy of Dr. Richard Ringel, Division of Pediatric Cardiology, The Johns Hopkins Hospital.)

Cardiac catheterization is performed routinely to assess patients with supravalvar stenosis when surgical repair is being considered. It is the only method for accurate measurement of the peak systolic gradient. Aortography distinguishes the localized type from diffuse hypoplasia and accurately defines the distal extent of narrowing (Fig. 78-13). Coronary ostial stenosis can also be detected; this is helpful in planning the surgical procedure.

## TREATMENT

Surgical repair of supravalvar AS is indicated in symptomatic patients as well as in asymptomatic patients with a peak catheter-measured systolic gradient greater than 50 mm Hg or an aortic annulus *Z*-score less than –3. The goals of repair are to relieve outflow obstruction and restore normal geometry to the aortic valve and sinuses of Valsalva. Expectant management of asymptomatic patients with lower LVOT gradients is acceptable since lesion regression has been documented in an important proportion of these patients coupled with a similar overall survival in patients treated with and without operative intervention.[82]

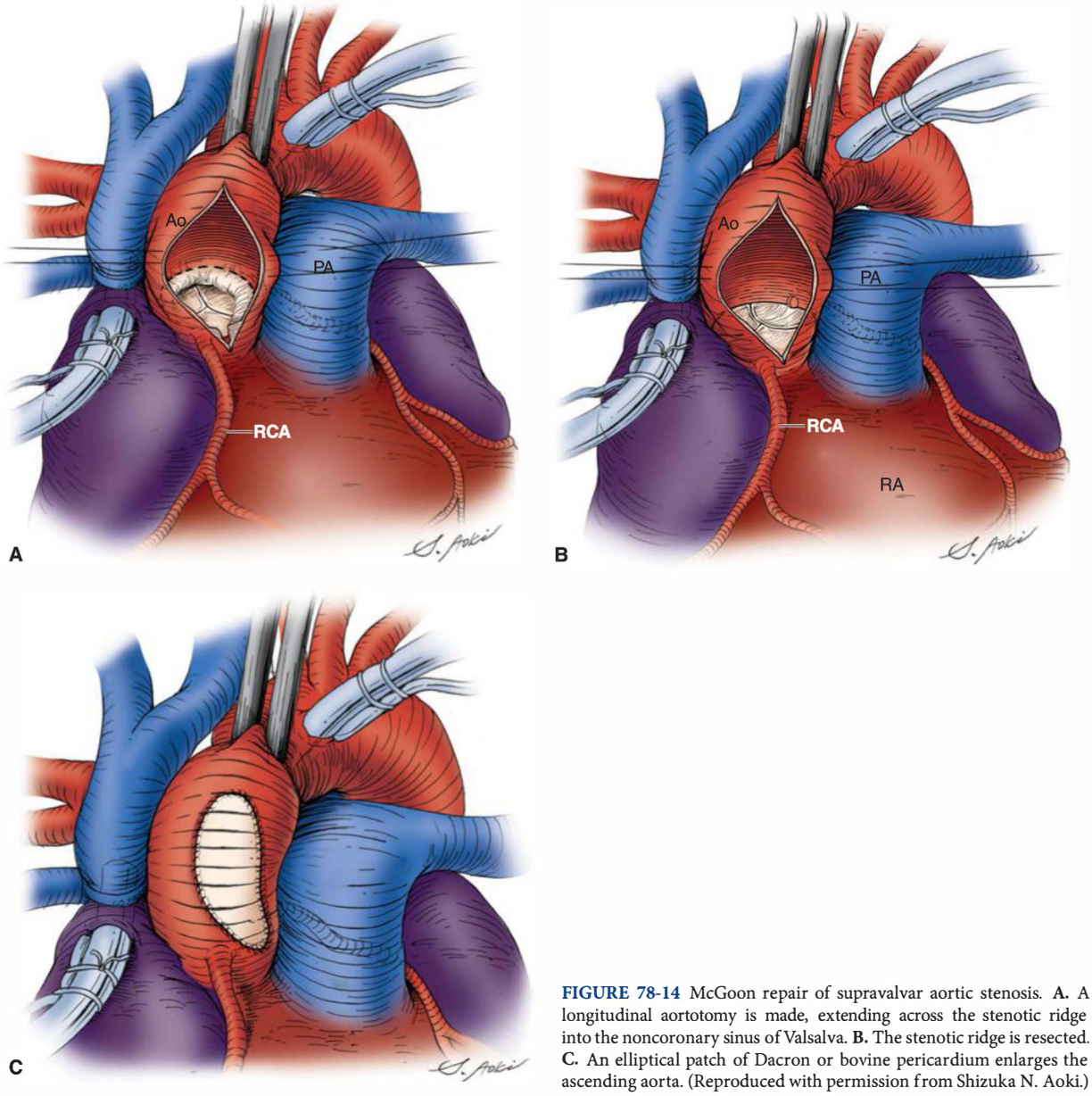



**FIGURE 78-14** McGoon repair of supravalvar aortic stenosis. **A.** A longitudinal aortotomy is made, extending across the stenotic ridge into the noncoronary sinus of Valsalva. **B.** The stenotic ridge is resected. **C.** An elliptical patch of Dacron or bovine pericardium enlarges the ascending aorta. (Reproduced with permission from Shizuka N. Aoki.)

The approach is via a median sternotomy. A single right-atrial cannula provides venous drainage, and the aortic cannula is placed as distally as possible. The aorta is clamped, and cardioplegia is delivered via the aortic root. Surgical repair techniques have evolved considerably since the first description by McGoon[83] in 1961, mainly in an effort to obviate distortion of the aortic root and sinuses and restore a more normal geometric configuration. McGoon and colleagues first performed a longitudinal aortotomy, beginning above the area of narrowing and extending into the noncoronary sinus of Valsalva (Fig. 78-14). The stenotic ridge is excised, and a diamond-shaped patch of bovine pericardium, Dacron, or Gore-Tex is used to augment the ascending aorta. With the recognition that distortion of the aortic valve and sinuses of Valsalva may contribute to outflow obstruction, techniques were developed to maintain greater symmetry of the sinuses. Doty and associates[84] described an inverted Y-incision into the noncoronary and right coronary sinuses of Valsalva (Fig. 78-15). The incision in the right sinus is placed well to the left of the origin of the right coronary artery. A pantaloon-shaped patch enlarges both the ascending aorta and the sinuses. Brom[85] advocated augmentation of all three sinuses (Fig. 78-16). The aorta is transected at the area of narrowing. Incisions are made into each sinus of Valsalva. The sinuses

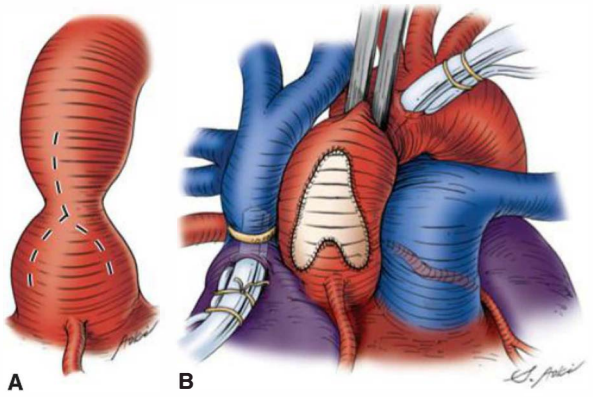



FIGURE 78-15 Doty repair of supravalvar aortic stenosis. **A.** An inverted Y-incision is made into the noncoronary and right sinuses of Valsalva. **B.** The aorta is augmented with a pantaloon-shaped patch. (Reproduced with permission from Shizuka N. Aoki.)

are augmented with triangular patches, and the augmented root is reanastomosed to the ascending aorta. To match in size the aortic root with the ascending aorta, and additional patch on the anterior aspect of the latter might be required. Myers and Waldhausen[86] described an innovative technique to achieve three-sinus augmentation using autologous tissue, termed the slide aortoplasty (Fig. 78-17). The aorta is transected at the area of narrowing, and incisions are made in the sinuses as with Brom's technique. Three incisions are made in the ascending aorta opposite the aortic valve commissures, and the aorta is reapproximated. Variations of this technique include excision of the stenotic segment[87] and the use of an autologous ring of PA to enlarge the sinuses.[88]

Regardless of the technique utilized, the coronary ostia should be inspected carefully to identify any obstruction that may be present. Treatment is based on the mechanism of obstruction. When ostial wall thickening is present, a Brom repair is used, with extension of the left coronary sinus incision into the left main coronary artery. Patch repair of the sinus is continued onto the coronary artery, with resultant coronary ostioplasty.[78,89] Coronary obstruction from leaflet adherence to the stenotic ridge is relieved by careful separation of the fused leaflet and resection of residual tissue around the ostium. Diffuse narrowing of the left main coronary artery requires coronary artery bypass. A saphenous vein graft may be preferable since progressive arteriopathy may involve the subclavian artery and limit internal mammary artery flow.[78]

Patients with diffuse hypoplasia pose a greater surgical challenge. A combination of the techniques discussed above must be tailored to the specific findings that are encountered.[90,91] Involvement of the transverse arch and descending aorta requires extensive augmentation using deep hypothermic circulatory arrest or low-flow bypass with continuous cerebral perfusion.[90–92]

It is difficult to assess the results of surgery for supravalvar AS because of the variability of pathologic findings, the diversity of the techniques employed, and the relatively small

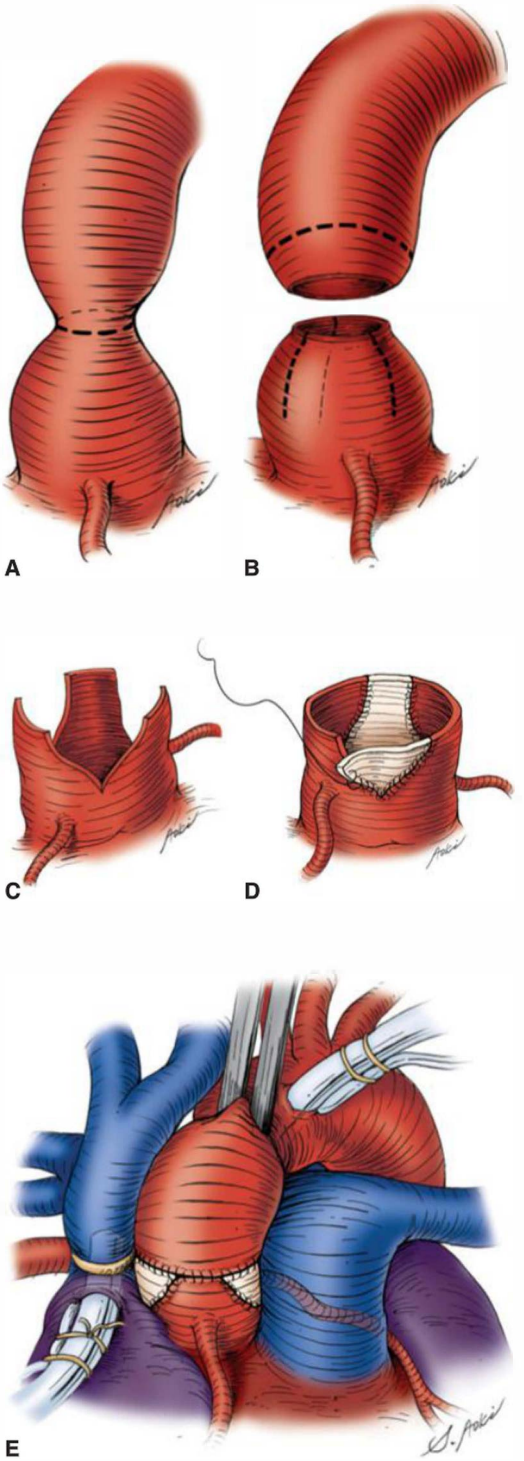



FIGURE 78-16 Brom repair of supravalvar aortic stenosis. **A.** The aorta is transected at the area of stenosis. **B.** Longitudinal incisions are made in each sinus of Valsalva. **C.** Appearance of the proximal aorta with incisions. **D.** Triangular patches augment the sinuses of Valsalva. **E.** The proximal aorta is reanastomosed to the distal aorta. (Reproduced with permission from Shizuka N. Aoki.)

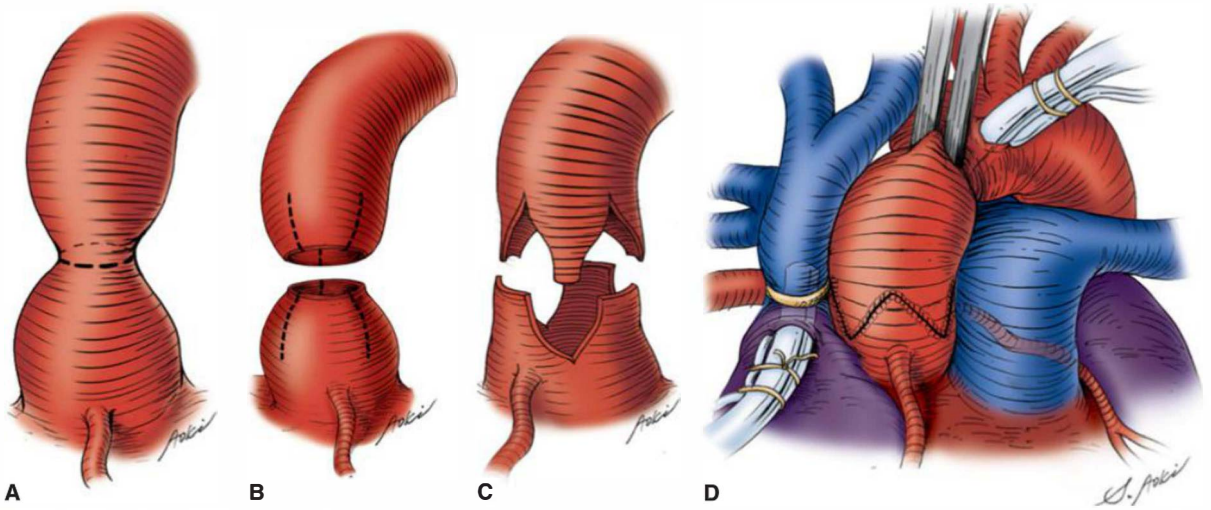



**FIGURE 78-17** Myers-Waldhausen repair of supravalvar aortic stenosis. **A.** The aorta is transected at the area of stenosis. **B.** Longitudinal incisions are made in each sinus of Valsalva. **C.** Longitudinal incisions are made in the ascending aorta opposite the aortic valve commissures. **D.** The proximal aorta is reanastomosed to the distal aorta. (Reproduced with permission from Shizuka N. Aoki.)

number of patients in each reported series.[93–97] Regardless of the technique, aortoplasty for localized obstruction achieves a long-term reduction of peak gradient from 90 mm Hg to 10 to 30 mm Hg with an early mortality of less than 2 percent.[73,77,93] No consistent differences in short- or long-term outcome were noted between techniques augmenting one, two, or all three sinuses of Valsalva, though Kaushal and colleagues[73,94,95] and Metton and colleagues[96] reported superior outcomes (less aortic insufficiency or stenosis, and reduced reoperation rate) with the Brom technique. Freedom from reoperation at 10 years is 70 to 85 percent, and 10-year actuarial survival is 90 to 95 percent.[76,77,94–96] Reoperation and late death most commonly are related to progressive valve dysfunction, not recurrence of supravalvar stenosis.[73,76,77] Surgery for diffuse supravalvar stenosis is less successful. Early mortality is greater than 10 percent, and rates of reoperation and late death also are increased.[98] Poor aortic growth persists in both the localized and the diffuse forms despite successful relief of obstruction, and so long-term serial monitoring is required.[99]

## SUMMARY

LVOTO is a common form of congenital heart disease that affects the aortic valve, the subvalvar region, and the supravalvar region. Severe stenosis results in left ventricular hypertrophy, cardiac failure, and sudden death. Early diagnosis (primarily by two-dimensional echocardiography) allows assessment of the level and severity of obstruction so that an appropriate plan of management can be designed. Surgery is indicated in symptomatic patients and in asymptomatic patients with moderate-to-severe obstruction or significant aortic regurgitation. Surgical techniques are available to relieve obstruction at all levels. The development of a replacement valve that has growth potential, resists degeneration, and does not require anticoagulation will improve outcomes and quality of life in this group of patients.

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## SURGERY FOR LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION IN CHILDREN BOARD REVIEW QUESTIONS (CHAPTER 78)

1. Regarding isolated severe tricuspid valvar aortic stenosis in a 16-year-old male who weighs 110 kg, all listed options would be acceptable surgical therapies EXCEPT:
   A. Replacement of the aortic valve with a mechanical prosthesis
   B. Repair of the aortic valve using surgical valvotomy of the fused right and noncoronary commissures
   C. Ross operation
   D. Replacement of the aortic valve with a bioprosthetic valve

2. A neonate presents with severe acidosis and hypotension. Echocardiogram demonstrates a bicuspid aortic valve with severe stenosis (gradient 70 mm Hg). The most appropriate next step in management is:
   A. Immediate transcatheter balloon valvotomy to relieve aortic obstruction and restore systemic perfusion
   B. Institution of prostaglandin, appropriate inotropic support, and further evaluation of the adequacy of the left-sided structures
   C. Cannulation for venoarterial support with ECMO
   D. Institution of prostaglandin and urgent surgical valvotomy

3. Surgical intervention for discrete aortic valvar stenosis is indicated when:
   A. The echocardiographic mean gradient is >40 mm Hg.
   B. The echocardiographic mean gradient is >25 mm Hg.
   C. There is left ventricular hypertrophy.
   D. There is concomitant aortic valvar insufficiency and stenosis.

4. The Ross operation has the following advantage compared to valve replacement with a bioprosthetic valve:
   A. The autograft possesses growth potential
   B. Absence of need for long-term anticoagulation
   C. Shorter cross-clamp and cardiopulmonary bypass time
   D. Reduced need for further intervention

5. A 100-kg 18-year-old active male is undergoing aortic valve replacement. During the operation, the aortic annulus is sized to 19 mm using calibrated sizers. The most reasonable next step is to:
   A. Implant a 19-mm prosthesis and separate from cardiopulmonary bypass
   B. Perform a posterior annular enlarging procedure and re-size the annulus
   C. Recannulate both vena cavae and perform a Konno aortoventriculoplasty
   D. Implant a 21-mm prosthesis in the supra-annular position

## ANSWERS

1. **Answer: B.** Repair of the aortic valve in isolated valvar stenosis, in the setting of a nonbicuspid valve, is unlikely to be successful. Aortic valvotomy can be tried as an initial strategy in the setting of discrete stenosis involving commissural fusion, but this patient has a trileaflet valve. All of the other listed interventions would be acceptable alternatives. Use of newer generation bioprosthetic valves have shown improved durability, and have made replacement a viable option even in young patients.

2. **Answer: B.** Although the neonate is in shock from severe aortic valvar stenosis, and likely would benefit from relief of the left ventricular outflow tract obstruction (whether surgically or using transcatheter methods), the adequacy of the left-sided structures to support the systemic circulation must be evaluated further with echocardiography. There are multiple predictive algorithms which have been published to assist with the decision making in neonatal critical aortic stenosis, including the "Critical Aortic Stenosis calculator" from the Congenital Heart Surgeons' Society, and the Rhodes' score. The initial management includes institution of prostaglandin to maintain ductal patency, support with inotropes, and resuscitation until the evaluation has been accomplished. ECMO may be required should initial stabilization be unsuccessful, but primary cannulation is not indicated.

3. **Answer: A.** Surgery is indicated when the mean echocardiographic gradient exceeds 40 mm Hg (severe stenosis), evidence of myocardial strain, ischemia on exercise testing, or in the presence of symptoms.

4. **Answer: A.** The bioprosthetic valve does not, obviously, possess growth potential. The Ross operation is technically more demanding and requires a longer cross-clamp and cardiopulmonary bypass time. Unfortunately, patients will require further intervention to replace the RV–PA conduit following a Ross operation, and may also require root replacement to relieve neoaortic dilation and associated neoaortic insufficiency. Newer generation bioprosthetic valves have improved durability compared to older valves, and therefore it is unlikely that patients will require a greater number of interventions to replace a bioprosthetic valve than those undergoing repeat RV–PA conduit interventions. Neither scenario, a Ross operation or a bioprosthetic valve, will require postoperative anticoagulation in the long term.

5. **Answer: B.** This patient is at significant risk for extreme patient–prosthesis mismatch if a 19-mm prosthesis is utilized. The best next step is to perform a posterior annular enlarging procedure such as the Manougian or Nicks procedure and resize the annulus. If the annular area can be enlarged sufficiently to accommodate an appropriately sized prosthesis for the patient's body surface area, this is the appropriate next step. Although a Konno procedure would certainly allow placement of an adequately sized prosthesis, it requires recannulation of both vena cavae and excessive intracardiac manipulation that may not be necessary in this case. Should the initial posterior enlarging procedures prove inadequate, a Konno procedure would be the appropriate next step.

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# Coarctation of the Aorta and Interrupted Aortic Arch

*Mark D. Rodefeld*

## KEY CONCEPTS

- **Coarctation of the aorta (CoA)**
  - Introduction
    - CoA is defined as a hemodynamically significant narrowing of the aorta. It occurs in about 4 in 10,000 births and accounts for more than 5 percent of congenital heart defects.
  - Clinical features
    - CoA presents as a spectrum of disease, ranging from neonatal ductal dependence to newly diagnosed, previously unrecognized, long-standing hypertension in an adult. One-third of neonates have an isolated CoA, one-third a ventricular septal defect (VSD), and one-third have complex congenital heart disease. A bicuspid aortic valve is present in 50 percent. Up to 80 percent of neonates with hypoplastic left heart syndrome have a CoA.
  - Diagnosis
    - Echocardiography is the diagnostic modality of choice in neonates. In older patients, computed tomography, magnetic resonance imaging and angiography are employed.
  - Treatment
    - Surgical treatment is preferred, with several techniques available. The choice of procedure depends on the anatomy of the aorta and associated anomalies. Native CoA balloon angioplasty is possible but has decreased long-term success in neonates; its use is perhaps of better application in desperately ill neonates and older children and recoarctation. Endovascular stents have emerged as a possible alternative to surgery, but long-term data are not available.
  - Results
    - Surgical repair of isolated CoA in the neonatal period can be accomplished with minimal morbidity and mortality, whereas the results of repair of CoA in association with complex congenital heart disease vary according to the dominant cardiac pathology and patient-related variables. Recoarctation occurs in up to 30 percent of patients corrected in the neonatal period, with a similar incidence despite the different techniques utilized. Late hypertension is common in patients operated later in life and is partly responsible for the slightly decreased long-term survival of this patient population.
- **Interrupted aortic arch (IAA)**
  - Morphology
    - In this condition there is anatomic lack of continuity in the aortic arch, classified according to the site of occurrence into type A (distal to left subclavian), type B (between the left common carotid and subclavian), and type C (just distal to the innominate artery). Type B is most common and is associated with thymic agenesis and 22q11 microdeletion. The prevalence of IAA is 0.003 per 1000 live births. A VSD is nearly always present. Bicuspid aortic valve is found in 50 percent of infants, with left ventricular outflow tract obstruction (LVOTO) often seen because of hypoplasia of the aortic root or posterior malalignment of the infundibular septum.
  - Clinical features
    - In newborns not prenatally diagnosed, presentation is rapid because of ductal closure and resulting visceral hypoperfusion and shock. Peripheral pulses vary according to the site of interruption and there is variable pulmonary overcirculation. Median time of death if untreated is between 4 and 10 days from birth, with 75 percent mortality within 1 year.
  - Diagnosis
    - Echocardiography is the diagnostic modality of choice in neonates. In more complex anomalies, computed tomography, magnetic resonance imaging, and angiography are employed.
  - Treatment
    - Surgical treatment follows a brief period of stabilization with prostaglandin ($PGE_1$) infusion

and restoration of ductal patency. Single-stage repair of aortic arch interruption and coexisting cardiac anomalies is then undertaken. Alternatively, a staged approach with initial arch repair and banding of the pulmonary artery followed by delayed correction of intracardiac anomalies can be considered.

- Results
  - In the current era, operative mortality following operative repair of an IAA is less than 10 percent. Five-year survival is reported at greater than 70 percent. Reintervention rates (surgical and percutaneous) for arch obstruction at 3-year follow-up range between 15 and 30 percent.

## COARCTATION OF THE AORTA

The term *coarctation* derives from the Latin *coarctare,* to compress. Coarctation of the aorta (CoA) is defined as a congenital narrowing of the aorta that is hemodynamically significant. CoA occurs in more than 4 in 10,000 live births and accounts for more than 5 percent of anomalies in children born with congenital heart defects.[1] Although isolated coarctation is more common in males, coarctation associated with other cardiac lesions occurs with equal frequency in males and females.

CoA can occur along the entire length of the aorta, but is most commonly located proximal to the junction of the ductus arteriosus and the descending aorta (Fig. 79-1). A posterior protuberance of the media, often augmented by ductal tissue, typically creates a "shelf" that protrudes into the aortic lumen. Externally, the aorta may be visibly narrowed, but often to a lesser extent than observed within the lumen. In addition, the aortic isthmus, defined as the segment between the left subclavian artery and the ductus arteriosus, is frequently hypoplastic. In some patients, hypoplasia may involve the entire transverse aortic arch. There are numerous classification systems, all of which are essentially descriptive.

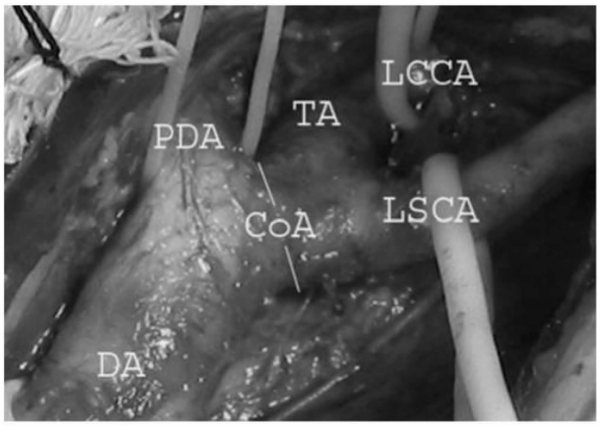



**FIGURE 79-1** Surgical photograph of aortic coarctation in an infant as seen through a left thoracotomy (operating surgeon's view). CoA, coarctation of aorta; DA, descending aorta; LCCA, left common carotid artery; LSCA, left subclavian artery; PDA, patent ductus arteriosus; TA, transverse arch.

The first description of aortic coarctation is credited to Paris in 1791, whereas the first published report of repair by resection and end-to-end anastomosis was by Crafoord in 1944.[2,3] Gross independently described a nearly identical repair in 1945 and was the first to describe the technique of interposition grafting.[4,5] Effective augmentation of the narrowed aortic segment with patch aortoplasty was described by Vossschulte in 1957, while Waldhausen introduced the subclavian flap aortoplasty in 1966.[6,7]

### Etiology

The etiology of aortic coarctation is unknown. Coarctation may be associated with genetic anomalies including Turner syndrome (45X,O) and Noonan syndrome; to date, however, no specific or reproducible molecular abnormality has been identified. In the fetal circulation, right-to-left flow through the ductus arteriosus results in decreased flow across the aortic isthmus with respect to either the ascending or descending aorta. Following postnatal ductal closure, the normal aorta presumably expands and grows in response to increased flow and pressure. This concept is corroborated by an increased incidence of CoA in patients with lesions associated with diminished aortic flow, such as aortic stenosis, ventricular septal defect (VSD), and mitral valve pathology. Furthermore, coarctation is rarely seen in lesions that result in increased aortic flow, such as tetralogy of Fallot.

It has been well recognized that the presence of ductal tissue within the aorta may contribute to this process. The muscular wall of the ductus arteriosus is exquisitely sensitive to changes in neonatal hemodynamics and to pharmacologic agents such as prostaglandin ($PGE_1$) and nonsteroidal anti-inflammatory agents. In some patients, ductal tissue extends well into the adjacent aortic wall and, during ductal contraction, may contribute to the development of coarctation. These findings have been confirmed in histologic studies.[8] Additional biochemical factors have been identified in patients with CoA. The aortic isthmus and, in some, the transverse arch exhibit a higher fraction of elastin lamellae and a lower fraction of α-actin-positive cells. These findings may account for decreased aortic growth.[9]

## Clinical Features

Clinical presentation is determined by the location and degree of aortic narrowing as well as the presence of associated intra- or extracardiac anomalies. Although neonates may appear normal at birth, they develop evidence of aortic obstruction with ductal closure. Manifestations include poor feeding, irritability, and tachypnea. A persistent systolic precordial murmur in the setting of weak or absent femoral pulses should raise the suspicion of aortic coarctation. Other presenting signs include differential oxygen saturations between upper and lower extremities and pulmonary overcirculation from left to right shunting across the patent foramen ovale. In the most severe form, with ductal closure over the first days to weeks of life, the sudden increase in afterload on the nonhypertrophied left ventricle results in a marked decrease in left-sided stroke volume and ejection fraction. Cardiomegaly results from an acute increase in right ventricular end-diastolic volume consequent to increased left-to-right shunting through the patent foramen ovale.[10] Poor perfusion and listlessness may occur. Femoral pulses are not palpable and metabolic acidosis ensues. If CoA is left untreated, end-organ damage (including renal failure and necrotizing enterocolitis) will ultimately result in death.

Infants who undergo more gradual closure of the ductus may develop arterial collaterals, allowing for a less catastrophic presentation. In such cases, the most common finding is usually failure to thrive. These children often have difficulty with feedings and diaphoresis. Physiologically, these infants have compensated for the increase in afterload and present with left ventricular hypertrophy. Older children and adults not diagnosed in infancy (presumably due to less severe disease) commonly present with unexplained hypertension or during the workup of a murmur. Lower extremity pulses are delayed or absent, exercise tolerance may be diminished, and claudication may be a chief complaint. Other symptoms include manifestations of upper body hypertension such as headache, epistaxis, visual field disturbances, and stroke.

## Associated Anomalies

In one report, 82 percent of all coarctations were isolated, 11 percent were associated with a VSD, and complex anatomy was observed in 7 percent.[11] CoA is associated with a bicuspid aortic valve in approximately 50 percent of patients.[12] Since CoA creates a pressure load on the left heart, a patent foramen ovale with a left-to-right shunt is often present. Aortic coarctation occurs in less than 10 percent of patients with transposition of the great vessels and in up to 50 percent of patients with the Taussig–Bing Anomaly (see Chapter 71).[13,14] In these patients, conal malalignment may produce subaortic obstruction with decreased antegrade flow through the transverse arch and isthmus. Hypoplastic left heart syndrome has an 80 percent incidence of CoA.[15] Coarctation is also associated with other forms of functional single ventricle, including tricuspid atresia with transposition of the great arteries and double-inlet left ventricle. Shone complex is characterized by a parachute mitral valve, supra-annular mitral ring, subaortic stenosis, and CoA. These patients present with a spectrum of disease, the most severe of which requires single ventricle palliation.

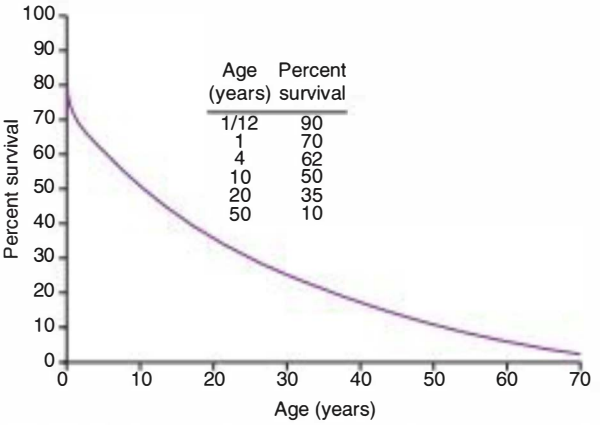



**FIGURE 79-2** Survival of patients with surgically untreated isolated coarctation of the aorta. (From Kouchoukos NT, Blackstone EH, Doty DB, et al. (eds). Coarctation of the aorta and interrupted aortic arch. In: *Kirklin/Barratt-Boyes: Cardiac Surgery,* 3rd ed. Philadelphia: Churchill-Livingstone, 2003:1328. With permission.)

## Natural History

Unrecognized CoA is rare in the current era. Untreated coarctation leads to premature death due to complications of unrelenting hypertension, with its attendant effects on the coronary and cerebral circulation. These effects include coronary artery disease, cerebrovascular accidents (both aneurysmal and atherosclerotic), congestive heart failure, and aortic rupture. In addition (particularly in patients with bicuspid aortic valves) bacterial endocarditis can occur. The survival of untreated patients with isolated CoA is depicted in Figure 79-2.

## Diagnostic Modalities

The principal method of diagnosis early in life is echocardiography. In the neonate and infant, the presence of a large thymus allows for excellent visualization of the arch structures (Fig. 79-3). Surface echocardiography provides specific anatomic information including location, length (diffuse versus discrete narrowing), and dimension of the coarctation segment. Severity of obstruction can be assessed quantitatively by measurement of Doppler flow velocity and qualitatively by evaluation of abdominal aortic pulsatility and diastolic flow. The presence of left ventricular hypertrophy also suggests increased severity. In addition, echocardiography allows for the detection of associated intracardiac lesions

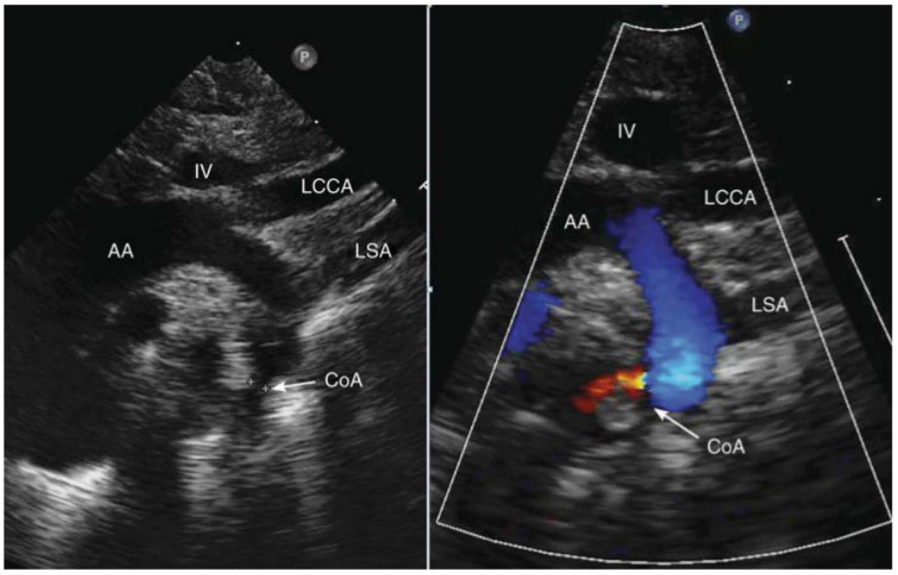



**FIGURE 79-3** Echocardiographic findings in aortic coarctation, with Doppler color imaging (right panel). AA, ascending aorta; CoA (with a rrow), coarctation of aorta; IV, innominate (left brachiocephalic) vein; LCCA, left common carotid artery; LSA, left subclavian artery. The innominate artery is not visible as off-axis in the two frames (Image used with permission of William Ravekes, MD, Johns Hopkins University.)

and transverse arch hypoplasia. In the presence of a patent ductus arteriosus, the ability of echocardiography to diagnose CoA may be limited. As thymic regression ensues, the interposition of lung tissue between the arch and the chest wall obscures echocardiographic details, making echocardiography less useful in older children and adults. In this particular age group, the use of cross-sectional imaging, such as thin-slice computed tomography and magnetic resonance imaging, provides excellent structural detail of the aortic arch and its branches. In addition, as these modalities provide imaging of the entire chest and abdomen, the detection of important collateral arteries is feasible.

Angiography (traditionally viewed as the "gold standard" for aortic evaluation) is now rarely used for diagnosis, as it is invasive and exposes the patient to a nephrotoxic contrast load (Fig. 79-4). However, angiography may be considered with the objective of delineating unclear anatomy and when percutaneous intervention is contemplated.

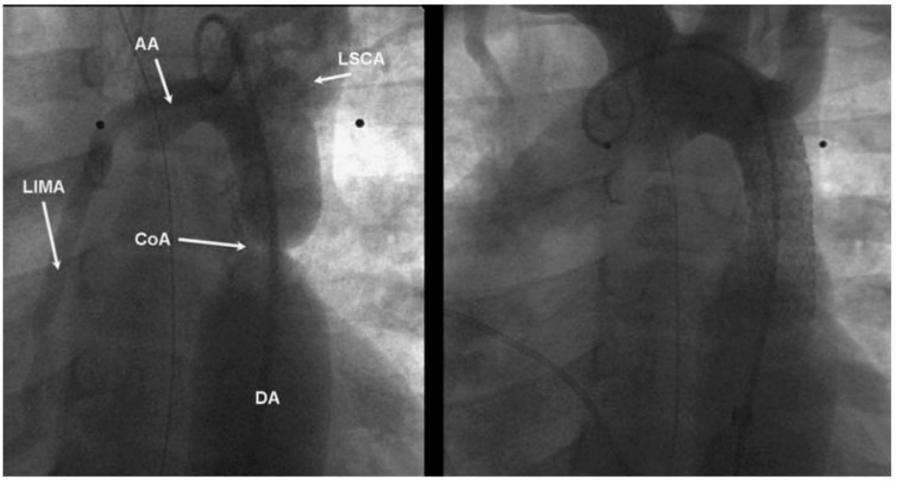



**FIGURE 79-4** Angiographic findings in aortic coarctation. AA, ascending aortic arch; TA, transverse aortic arch; DA, descending aorta; IA, innominate artery; LCCA, left common carotid artery; LSCA, left subclavian artery; CoA, coarctation of aorta. (Image courtesy of Richard Ringel, MD, Division of Pediatric Cardiology, The Johns Hopkins Hospital.)

## Medical Therapy

The role of medical therapy in the treatment of hemodynamically significant CoA is limited to temporizing measures while the timing and method of surgical repair are being considered. The mainstay of medical therapy in neonates is intravenous PGE1 infusion. This maintains patency of the ductus arteriosus, allowing for resuscitation and restoration of end-organ perfusion in compromised infants. Side-effects of $PGE_1$ include generalized edema, hypotension and apnea, sometimes requiring preoperative mechanical ventilation.

In patients who have undergone repair and in those in whom the diagnosis is made later in life, the surveillance and treatment of hypertension is paramount.

## Catheter-Based Intervention

Successful primary treatment of aortic coarctation by balloon angioplasty has been reported but requires further investigation to define its overall efficacy, safety, and long-term durability. The main limitations of balloon angioplasty, particularly in the neonate, are early recurrence of coarctation, aneurysm formation, and access-related injury to the femoral artery. In a recent retrospective review, nearly 60 percent of neonates undergoing primary balloon angioplasty required subsequent surgical repair, and 13 percent developed saccular aneurysms. In the surgical repair group, 18 percent developed recoarctation responsive to balloon dilatation, and no patients developed aneurysms.[16] Balloon angioplasty has a limited role in critically ill neonates who are poor surgical candidates because of severe left ventricular dysfunction or intercurrent illness, allowing for palliation until surgical correction can be safely undertaken. Balloon angioplasty is nevertheless the treatment of choice for recurrent coarctation following neonatal surgical repair, with a greater than 90 percent success rate at relieving the gradient and a 16 percent incidence of restenosis requiring reintervention.[17]

Endovascular stents provide durable relief of aortic coarctation in older children and adults. Stents have a significant advantage over simple angioplasty in that they prevent elastic recoil of the aortic wall, reducing the likelihood of dissection during the procedure. Stent placement in younger children, however, is generally not preferable. Smaller stents cannot undergo serial dilation to keep pace with somatic growth, resulting in the eventual need for a technically difficult surgical repair. Larger stents may allow serial dilatation, but the size of the femoral artery often precludes stent placement in smaller patients. As with surgical intervention, persistent hypertension despite successful relief of obstruction requires diligent surveillance and treatment. In a review of endovascular treatment of CoA in adolescents and adults (1-year follow-up), all patients had persistent resolution of their aortic gradient, with a 13 percent incidence of small aneurysms.[18] Although long-term data are not yet available, midterm results appear to compare favorably with surgical repair.

## Surgical Therapy

Surgical correction is indicated for all symptomatic neonates and infants, as well as older children and adults who are not candidates for transcatheter therapy. Operation should be considered in asymptomatic patients for an upper-to-lower extremity mean blood pressure gradient in excess of 20 mm Hg that is associated with upper extremity hypertension and a greater than 50 percent reduction in luminal diameter in the coarctation segment. A low gradient in the presence of robust collateral development does not exclude severe obstruction and should not be considered a contraindication to surgery.

Following induction of general anesthesia, a right radial arterial line is inserted and the patient is placed in the right lateral decubitus position (for left-sided descending aorta). A left posterolateral thoracotomy through the fourth intercostal space provides ideal exposure for most repairs. Alternatively, a muscle-sparing extrapleural approach can provide adequate exposure with comparable results.[19] In cases requiring associated intracardiac repair or complex transverse arch reconstruction, median sternotomy and cardiopulmonary bypass with circulatory arrest may be utilized; a description of these more complex techniques is beyond the scope of this discussion. Following thoracotomy, the lung is retracted anteroinferiorly and the pleura overlying the aorta and left subclavian artery is incised longitudinally. If present, a supreme intercostal vein and any crossing lymphatics are ligated and divided to prevent the occurrence of a chylothorax. Care is taken to preserve the left vagus nerve and the recurrent laryngeal nerve as it passes around the ligamentum arteriosum or PDA. The pleural edges are suspended by sutures to aid in exposure and retraction of the lung (Fig. 79-5). For all methods of reconstruction, dissection and control of the proximal aortic arch, left common carotid and subclavian arteries, descending aorta, ductus

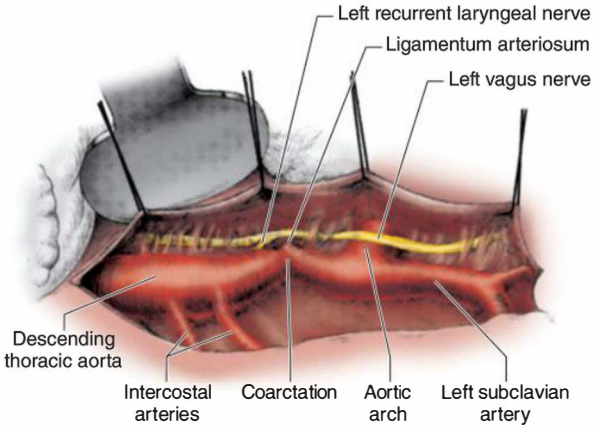



**FIGURE 79-5** Surgical anatomy of a coarctation of the aorta. (From Khonsari S, Sintek CF. *Cardiac Surgery: Safeguards and Pitfalls in Operative Technique,* 3rd ed. Philadelphia: Lippincott, Williams & Wilkins, 2003:188. With permission.)

arteriosus, and intercostal arteries is essential for safe repair. Although it is preferable to preserve the intercostal arteries when possible, several pairs may be sacrificed to obtain a tension-free anastomosis.

## RESECTION WITH END-TO-END ANASTOMOSIS

The ductus arteriosus is ligated and divided. The proximal aorta is clamped obliquely across the left subclavian artery and transverse aortic arch. The distal aorta is clamped well below the planned resection and anastomotic site. In young patients, the left common carotid artery may be safely occluded by the proximal clamp, but the innominate artery must remain patent to preserve cardiac output and cerebral blood flow. This is confirmed by an adequate waveform on the right radial artery pressure monitor and maintained cerebral infrared spectroscopy data (NIRS). In older patients, occlusion of the left common carotid artery may be inadvisable. Care is taken to ensure that the clamps do not distort the area of reconstruction or compress the innominate artery. Intercostal arteries that backbleed into the field should be controlled by temporary clips or snares. The coarctation segment is completely resected, including all ductal tissue macroscopically visible within the aorta. The aorta is then reapproximated in a running fashion using 7-0 suture in neonates and small infants (Fig. 79-6). Interrupted suture placement or the use of absorbable suture material has not been shown to improve results. Generally, a clamp time of less than 30 minutes is felt to be safe. Mild hypothermia is employed by many groups to reduce the risk of spinal cord ischemia.

The primary advantage of resection and end-to-end anastomosis is the complete excision of all abnormal aortic tissue. However, adequate mobilization is required to create a tension-free anastomosis. Mobilization of the distal aorta risks injury to fragile intercostal and collateral vessels in older children and adults. Other techniques of repair may therefore be more appropriate in this age group.

Extended resection with end-to-end anastomosis is necessary in the presence of severe transverse arch hypoplasia. The proximal clamp is placed to the level of the innominate artery and ascending aorta. After the coarctation segment is resected, the underside of the aortic arch is spatulated and anastomosed to the appropriately beveled descending aorta (Fig. 79-7). This results in a larger effective anastomotic

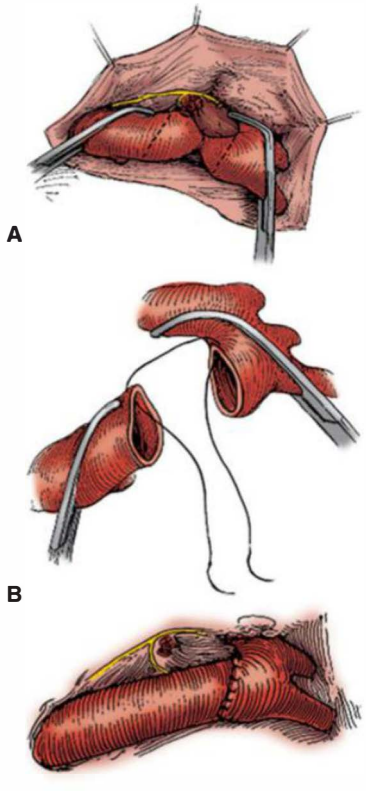



**FIGURE 79-6** Resection of aortic coarctation segment with end-to-end anastomosis. **A.** Proximal and distal control of the aorta is obtained and the ductus is ligated. **B.** The coarctation is resected. The aorta is reapproximated using fine polypropylene suture. **C.** Completed aortic reconstruction. (Reprinted with permission from Shen I, Ungerleider RM. Coarctation of the aorta. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

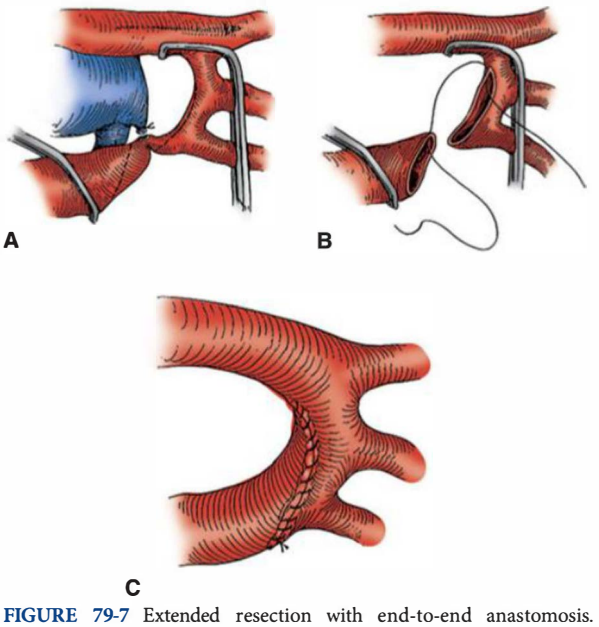



**FIGURE 79-7** Extended resection with end-to-end anastomosis. **A.** The proximal aortic clamp is placed flush on the innominate artery at the level of the ascending aorta. The ductus is ligated, the coarctation is resected, and the underside of the aortic arch is incised. **B.** The descending aorta is beveled and enlarged in order to appropriately augment the aortic arch. Reconstruction is carried out using fine polypropylene suture. **C.** The completed repair. (Reprinted with permission from Shen I, Ungerleider RM. Coarctation of the aorta. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

orifice area. Extensive proximal and distal mobilization is necessary to allow tension-free approximation.

### SUBCLAVIAN FLAP AORTOPLASTY

Full mobilization of the left subclavian artery is required for this repair. The left subclavian artery is ligated at the level of its first branch, taking care to preserve all distal branches, as they provide the collateral circulation to the left arm. Some surgeons additionally ligate the vertebral artery to prevent late subclavian steal syndrome. The ductus is ligated and a longitudinal aortotomy is begun distal to the area of coarctation. The incision is extended proximally across the coarctation site and into the left subclavian artery, ending just proximal to the previously placed ligature. The left subclavian artery is only then transected and the resulting subclavian flap is turned inferiorly and sutured to the edges of the descending aorta (Fig. 79-8). A "reverse" subclavian flap may be used less commonly for discrete coarctation proximal to the left subclavian artery or distal transverse arch hypoplasia (Fig. 79-9). A reverse subclavian flap aortoplasty can also be combined with an end-to-end anastomosis to address distal arch and isthmic hypoplasia in the setting of coarctation.

The advantages of subclavian flap aortoplasty include ease of repair and the avoidance of extensive aortic mobilization. Adequate length and caliber of the subclavian artery should be ascertained when considering this technique. Subclavian flap aortoplasty is generally avoided beyond infancy because of concern with upper extremity perfusion.

### PATCH AORTOPLASTY

Following clamp placement, the aorta is incised longitudinally across the coarctation, from the left subclavian artery origin to the level of the first intercostal artery (Fig. 79-10). The coarctation ridge is typically not excised, and an oval patch of prosthetic material is fashioned and sutured to the aortotomy margin using continuous suture technique. Care is taken to ensure that the widest portion of the patch overlies the coarctation ridge.

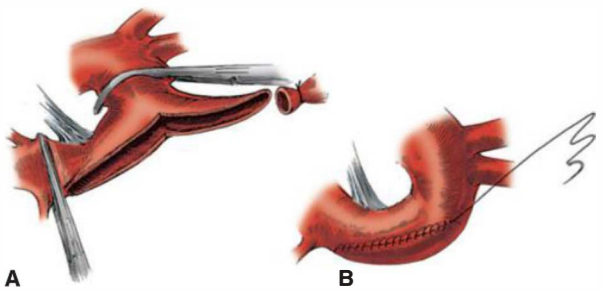



**FIGURE 79-8** Subclavian flap aortoplasty. **A.** The transverse arch and descending aorta are clamped. An aortotomy extends from the descending aorta across the coarctation into the left subclavian artery. **B.** The left subclavian artery is sewn over the isthmus of the aorta using a continuous 7-0 polypropylene suture. (From Aortic coarctation. In: Casteneda AR, Jonas RA, Mayer JE, Hanley FL (eds). *Cardiac Surgery of the Neonate and Infant*. Philadelphia: Elsevier, 1994:347. With permission.)

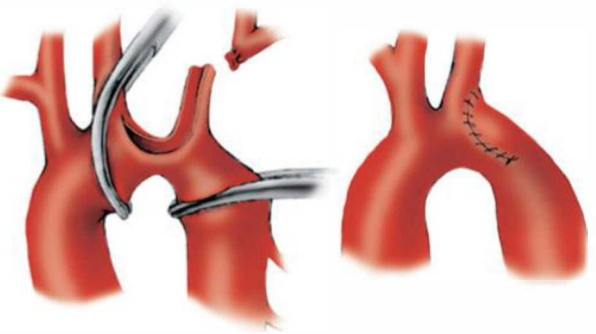


**FIGURE 79-9** Reverse subclavian flap aortoplasty. The left subclavian artery is divided at its first branch (left). An incision is made on the medial aspect of the subclavian artery extending across the superior transverse arch to the origin of the left common carotid artery. The subclavian artery flap is turned medially to augment the transverse aortic arch (right). (From Khonsari S, Sintek CF. *Cardiac Surgery: Safeguards and Pitfalls in Operative Technique*, 3rd ed. Philadelphia: Lippincott, Williams & Wilkins, 2003:188. With permission.)

The advantage of this technique is that it is relatively expedient and can be performed with minimal dissection of collaterals, particularly in the older patient in whom mobilization and a tension-free anastomosis might not be easily achieved. Furthermore, the patch can cover a relatively long coarctation segment and can be made sufficiently redundant to limit the risk of recoarctation. The recoarctation rate is very low, particularly in children above 1 year of age.

The main disadvantage of patch aortoplasty is aneurysmal dilatation in the aortic wall opposite the patch. Rates of aneurysm formation varied widely but in some series have occurred in over 50 percent of patients.[20] It is now recognized that this complication was largely related to the use of Dacron as the patch material in earlier series. The noncompliant quality of Dacron generated excessive tension in the aortic wall opposite the patch.[21] This was accentuated in patients in whom the coarctation ridge was excised. Currently, polytetrafluoroethylene is the prosthetic material of choice for patch aortoplasty. A recent series reported no true aneurysm formation in 125 patients between the ages of 4 days and 17 years.[22]

In older children and adults, where somatic outgrowth is not a concern, interposition grafting can be performed with a technique similar to that described for thoracic aortic aneurysms.

## Management of Associated Anomalies

In patients with complex associated lesions (e.g., transposition of the great arteries, double-outlet right ventricle), the approach and timing of coarctation repair is usually dictated by the management of the more complex anatomy.

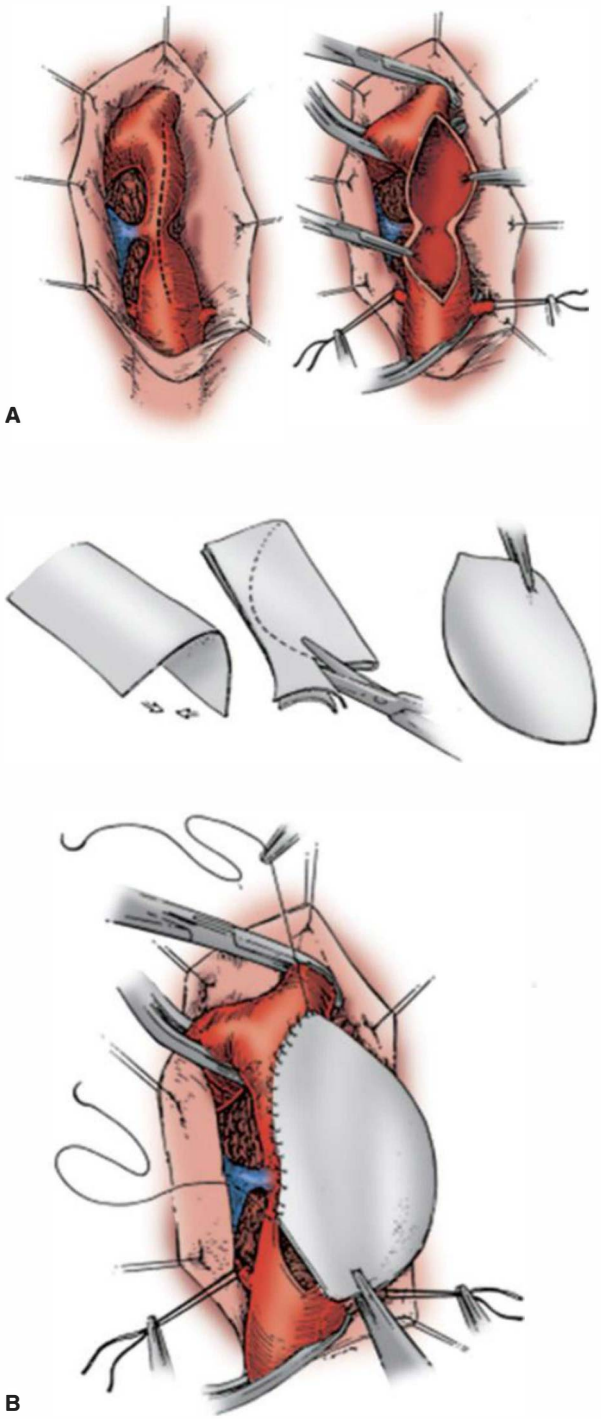



**FIGURE 79-10** Patch aortoplasty. **A.** The aorta is incised longitudinally (dotted) line after obtaining proximal, distal and branch control. The coarctation ridge is left in situ. **B.** An oval patch of polytetrafluoroethylene is fashioned and sutured in place using a continuous suture, ensuring substantial redundancy to allow for growth. (From Backer CL, Paape K, Zales VR, et al. Coarctation of the aorta: Repair with polytetrafluoroethylene patch aortoplasty. *Circulation* 1995;92:132. With permission.)

This typically entails repair via median sternotomy with hypothermic circulatory arrest or low-flow continuous cerebral perfusion. Coarctation repair is performed by patch aortoplasty or resection and extended end-to-end anastomosis.

The management of CoA associated with a VSD remains controversial. Patients with VSDs that are likely to cause congestive heart failure, unlikely to close spontaneously, and have favorable anatomy, may benefit from a single-stage repair of both VSD and coarctation via median sternotomy. Gaynor and colleagues advocate simultaneous repair for all infants with aortic coarctation, moderate-to-large VSDs, and aortic arch hypoplasia.[23] In their retrospective series, median survival at 16 months was 96 percent (actuarial 3-year survival), with actuarial freedom from all reintervention of 71 percent at 1 year and 59 percent at 2 years. Alternatively, some centers advocate pulmonary artery banding at the time of coarctation repair via left thoracotomy. Closure of the VSD and removal of the pulmonary artery band is performed via median sternotomy at 4 to 6 months of age. A multi-institutional study reported a 97-percent 2-year survival in patients undergoing two-stage repair. In this group of 34 patients, 38 percent had undergone subsequent VSD closure and 9 percent had expired, leaving 53 percent free from further surgery at 2-year follow-up.[24] New technologies, such as absorbable pulmonary artery bands and catheter-guided septal occluders, may increase the potential benefits of a two-staged approach.

## Postoperative Management and Early Complications

In the absence of complex congenital heart disease, postoperative management focuses on pain control and pulmonary toilet, as would be expected after any thoracotomy. In neonates, careful monitoring is essential, particularly as this group has a higher incidence of apnea and lobar collapse. Arterial hypertension following repair is common and independent of pain control. So-called paradoxical hypertension can persist for days to weeks following repair and may be related to increased catecholamine levels in a sensitive vascular bed coupled with an overstimulated renin-angiotensin axis. Age-appropriate antihypertensive agents are used carefully in order to avoid hypotension. Five to ten percent of older patients will report abdominal discomfort for a few days following coarctation repair ("postcoarctectomy syndrome"). This is mild in most cases but in some may require a period of bowel rest and nasogastric decompression. The most malignant form of this process can lead to necrotizing mesenteric arteritis requiring bowel resection. Aggressive management of hypertension appears beneficial. Chylothorax may occur secondary to lymphatic leak from mediastinal dissection. Tube thoracostomy drainage should be carefully monitored for chylous characteristics, and clinically significant late pleural effusions should be evaluated by thoracentesis.

Conservative management predominates. Rarely, reoperation for ligation of lymphatics is required. The most feared complication of coarctation repair is paraplegia, with an incidence of up to 0.5 percent in some series.[25] A number of contributing factors have been identified, including cross-clamp time (greater than 30 min), division of arterial collaterals during dissection, and intraoperative hypotension, among others. The recognition of these factors has resulted in a decreased incidence of paraplegia in the modern era. Preventive measures may include somatosensory evoked potential monitoring, especially in older patients presenting with coarctation.

## Operative Mortality

The development of modern neonatal intensive care has shown a positive impact on the results of surgery for aortic coarctation. Most patients arrive in the operating room in stable condition and are closely monitored in the immediate postoperative period. Although early and late morbidity may occur, perioperative mortality remains rare. Serfontein and Kron reported neonatal mortality of 1.2 percent, and this was directly related to the presence of preoperative instability.[26] In older patients the operation is even safer unless CoA is accompanied by significant associated anomalies.

## Long-Term Results

The development of long-term complications is not rare.[27] Table 79-1 summarizes key long-term sequelae, their incidence, and considerations regarding their etiology.

### HYPERTENSION

Hypertension is frequently reversed immediately following repair. Unfortunately, there is a significant incidence of late postoperative hypertension independent of recurrent coarctation, which may account for many of the long-term sequelae in these patients. The etiology of hypertension is multifactorial. At least some component is a result of renin overactivity, as renal perfusion is limited by the coarctation. Other contributing factors include deranged baroreceptor and endothelial function and abnormal arterial wall stiffness in the upper extremities.[28] The result is a poorly defined vasculopathic state associated with persistent hypertension throughout life. The roles of prenatal hemodynamics and delayed early treatment are also unknown.

### RECURRENT COARCTATION

Recurrence of aortic coarctation is a process largely limited to repairs performed in the neonate. The overall recurrence rate depends on the original morphology, patient's age and weight at repair, associated anomalies, type of repair used, and vigilance of postoperative surveillance. Most centers use the same criteria for recurrence as with initial diagnosis: a pressure gradient across the lesion of greater than 20 mm Hg. The recurrence rate in neonates weighing less than 2 kg may be as high as 44 percent,[29] but it is between 15 and 20 percent overall.[16,30] There is a 2 percent recurrence rate following coarctation repair in adults.[31]

### ANEURYSM FORMATION

As discussed above, the development of aneurysms following patch repair with a polyester prosthetic patch has been

**TABLE 79-1: Risk Factors for Complications Following Repair of Coarctation of the Aorta**

| Complication | Prevalence (%) | Cause of Death (%) | Risk Factors |
|---|---|---|---|
| Coronary artery disease | 5–23 | 25–66 | Duration of preoperative hypertension<br>Postoperative hypertension |
| Hypertension | 25–75 | – | Age at repair<br>Recoarctation<br>Follow-up duration<br>Aortic insufficiency |
| Cerebrovascular accident | 3 | 0–12 | Pre- and postoperative hypertension<br>Berry aneurysm |
| Heart failure | Unknown | 9–35 | Hypertension<br>Aortic valve disease<br>Coronary artery disease |
| Recoarctation | 3.1–10.8 | – | Repair in infancy<br>Subclavian flap aortoplasty<br>Balloon angioplasty |
| Aneurysm/rupture | 5.4–20 | 5–35 | Patch aortoplasty<br>Balloon angioplasty |

Adapted from Jenkins NP, Ward C. Coarctation of the aorta: Natural history and outcome after surgical treatment. *Q J Med* 1999;92:365. With permission.

well described. In addition, pseudoaneurysm formation along suture lines has been reported. These can become further complicated if they are mycotic.

### LATE MORTALITY

The true incidence of long-term mortality directly related to CoA is difficult to determine. Heterogeneity of patient groups, loss to follow-up, and the underdetection of hypertension-related deaths preclude simple analysis. In the perioperative period, mortality is less than 3 percent, and is more than likely independent of technique of repair.[23,32] More important to the survival of these patients is the presence or absence of complex congenital heart disease. Late mortality appears to be related to the sequelae of uncontrolled hypertension, such as congestive heart failure, cerebrovascular events, and aortic dissection or rupture.[26]

## Conclusions

Aortic coarctation presents in a diverse population, ranging from critically ill neonates with complex congenital anatomy to adults with newly diagnosed refractory hypertension. The efficacy of surgical therapy is well established, with several acceptable techniques for resection and repair being available. The presence of associated congenital anomalies is the largest risk factor for both prognosis and mortality. Catheter-based interventions may be appropriate in some older patients, but surgical repair remains the treatment of choice for the majority of patients with aortic coarctation.

# INTERRUPTED AORTIC ARCH

Interrupted aortic arch (IAA) describes a congenital cardiovascular malformation involving an anatomic lack of continuity between the proximal and distal components of this vascular structure. Unlike coarctation, it is a complete disruption of the aorta. It is frequently associated with presence of a VSD and a spectrum of hypoplasia of left-sided heart structures secondary to limited left heart outflow in fetal life. In addition, there is an association with microdeletion of the q11 segment of chromosome 22, which may involve issues of developmental delay and cognitive sequelae.

IAA comprises 1 to 4 percent of autopsy cases of congenital heart disease and represents 1.3 percent of infants presenting with congenital cardiovascular disease. The estimated prevalence is 0.003 per 1000 births.[33] Untreated, this uncommon anomaly has a median age at death between 4 and 10 days, with a 75 percent mortality within 1 month.[34] Death occurs with closure of the ductus arteriosus. If the ductus remains open longer, survival is possible; however, mortality is then 90 percent by 1 year.[35]

This malformation was first described by Steidele in 1778.[36] Surgical intervention was first described by Merrill in 1955, where a direct anastomosis was performed in a patient with short segment IAA.[37] An associated VSD was not closed at the time of repair. By 1959, Celoria and Patton had collected 28 cases that were classified according to site of obstruction.[38] Villalobos and colleagues as well as Blake and colleagues each reported a successful case during the early 1960s, in which they employed a prosthetic graft for repair.[39,40] Sirak and colleagues were the first to describe the use of "turned down" arch vessels in the reconstruction as well as the first neonate to survive this repair.[41] Barratt-Boyes and coworkers in 1970 performed the first simultaneous repair of aortic arch interruption and VSD closure.[42] This procedure was performed using deep hypothermic circulatory arrest via thoracotomy and median sternotomy. The first simultaneous IAA and VSD repair via the anterior approach and without use of a prosthetic graft was reported by Trusler in 1975.[43] The treatment of IAA was revolutionized with the introduction of $PGE_1$ in 1976 by Elliot and colleagues.[44]

## Embryology

The aortic arch is described anatomically as having proximal and distal components. In early fetal development, there are six aortic arches. These connect with the right and left dorsal aortas distally (descending aorta) and with the conotruncus proximally (proximal aorta). Arches I to III subsequently regress to become facial and skull vessels.[45]

In normal embryogenesis, the proximal aortic arch originates from the left horn of the aortic sac to develop the portion between the innominate and left carotid arteries. The distal arch (between the left carotid and left subclavian arteries) is derived from the left fourth aortic arch. The aorta between the left subclavian artery and the ductus arteriosus is derived from the confluence of the dorsal aorta and the left sixth arch. The site of interruption is associated morphologically with a specific abnormality in the development of these aortic arches.[45]

## Morphology and Classification

Celoria and Patton introduced a classification system for IAA in 1959 (Fig. 79-11).[38] Type A interruption was described as occurring distal to the left subclavian artery. In this subset, the interruption yields a duct-dependent environment for lower-body perfusion. This form of IAA has also been described as "aortic atresia" and classically presents with a fibrous cord with no luminal continuity spanning the interruption. The length of interruption may vary and can approach up to 3 cm in some cases. Type B interruption occurs between the left common carotid artery and the left subclavian artery. It is the most common type of IAA, with an approximate incidence of 60 to 70 percent.[46] It is important to note that type B IAA can be associated with an aberrant right subclavian artery originating from the distal descending thoracic aorta. This associated anomaly is correlated with the nomenclature of

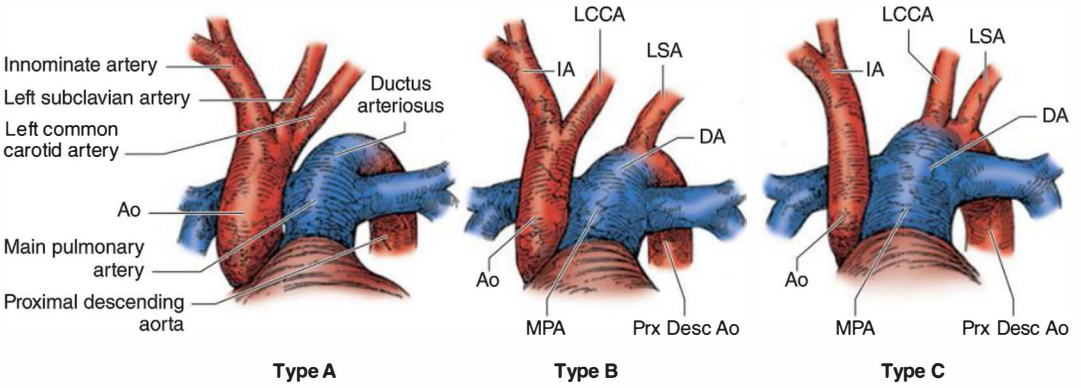



**FIGURE 79-11** Celoria and Patton morphologic classification of aortic arch interruption, according to the site of anatomic discontinuity along the arch. (From Jonas RA. Interrupted aortic arch. In: Mavroudis C, Backer CL (eds). *Pediatric Cardiac Surgery,* 3rd ed. Philadelphia: Mosby, 2003:345–359. With permission.)

type $B_1$ versus type $B_2$ IAA. Type B IAA is also the specific subtype associated with DiGeorge syndrome and 22q11 microdeletion. Type C interruption is found between the innominate artery and left common carotid artery. It is the rarest form, comprising less than 5 percent of IAAs.[47]

## Associated Cardiac Anomalies

Anomalies of the brachiocephalic vessels are relatively common. As mentioned, an aberrant right subclavian artery originating as a fourth brachiocephalic branch from the descending thoracic aorta is common in type B but may also be found in type A IAA. Other abnormal origins of the right subclavian artery include a cervical takeoff from the right common carotid artery or from a right-sided ductus, which itself is originating from the right pulmonary artery.[48]

The aortic valve is bicuspid in approximately 30 to 50 percent of patients with IAA, as is the case with aortic coarctation. Subaortic stenosis may be present or may develop later, especially in cases involving type B IAA and an aberrant origin of the right subclavian artery. This is due to the increased flow via the ductus arteriosus during fetal development and less flow via the left ventricular outflow tract (LVOT).[34]

A coexisting large VSD is nearly always present. Aside from a PDA, it is the most common associated anomaly, occurring in approximately 75 percent. This anatomic anomaly (with the septum frequently being malaligned and displaced posteriorly) creates a large muscular ridge known as the muscle of Moulaert.[34,49] This structure may protrude into the subaortic region, resulting in left ventricular outflow tract obstruction (LVOTO).

An atrial septal defect can also be seen in association with IAA. It is usually of the patent foramen ovale variety but can at times be large and thus physiologically significant. Other lesions such as truncus arteriosus (common arterial trunk), transposition of the great arteries, or aortopulmonary window may coexist.

## Clinical Presentation and Diagnosis

Via ultrasound evaluation, prenatal diagnosis has become common. Infusion of $PGE_1$ is initiated immediately following birth. In infants in whom a diagnosis has not been made prenatally, clinical sequelae are often not present until ductal closure. Subsequently, generalized tissue malperfusion and profound associated acidosis is typical. End-organ issues such as liver dysfunction with elevated hepatic enzymes, kidney failure with anuria, and ischemic gut injury with necrotizing enterocolitis may occur. Myocardial and cerebral injury may also be present due to prolonged systemic acidosis. In cases where ductal closure does not occur, symptoms of congestive heart failure may result, as a consequence of increasing left-to-right shunt via the VSD as pulmonary resistance falls.[50]

Clinical examination findings include abnormal pulses, depending on the location of the interruption. Differential cyanosis between upper and lower extremities is not often present or conclusive. Cardiac murmurs and electrocardiograms are also nonspecific. Chest radiographs may reveal gross cardiomegaly as well as pulmonary congestion.

Echocardiography, the only specific diagnostic modality, is required prior to operative intervention (Fig. 79-12). Cardiac catheterization, which is challenging in neonates presenting in shock, is no longer considered a requirement for diagnosis unless unusual anatomic features require further definition. Using transthoracic echocardiography, the exact site of aortic arch interruption as well as the presence of an associated VSD can typically be determined. In addition, evaluation of the LVOT as well as any other coexisting intracardiac anomalies can be satisfactorily performed. Additional specific data such as the length of interruption, luminal diameter of the aorta, exact dimensions of the LVOT, anatomy of the aortic valve, and presence or absence of thymic tissue are helpful in designing a therapeutic strategy. Body imaging techniques, such as computed tomography and magnetic resonance imaging (Fig. 79-13), can be useful in difficult cases and to aid in surgical planning.

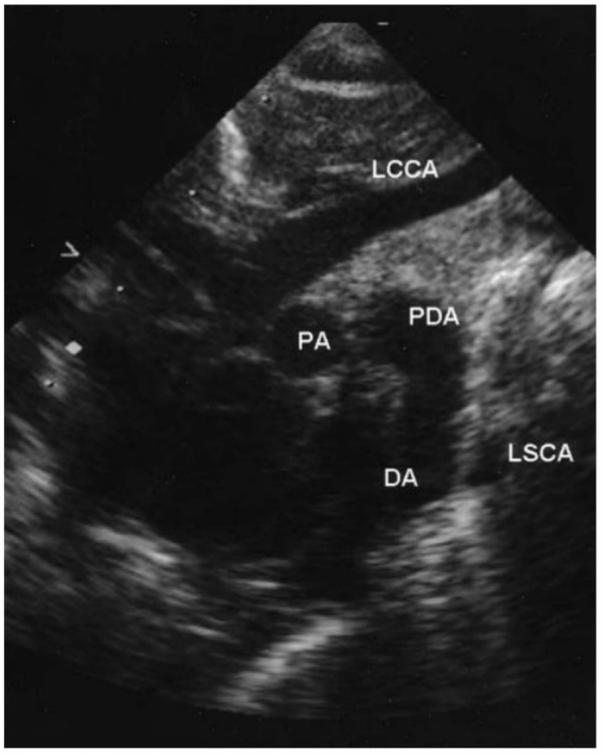



**FIGURE 79-12** Echocardiographic findings in aortic arch interruption type B. No continuity in the arch is noted echocardiographically between the takeoff of the left common carotid and subclavian arteries. AA, ascending aorta; DA, descending aorta; IA, innominate artery; LCCA, left common carotid artery; LSCA, left subclavian artery; PDA, patent ductus arteriosus. (Courtesy of William Ravekes, MD, Division of Pediatric Cardiology, The Johns Hopkins University.)

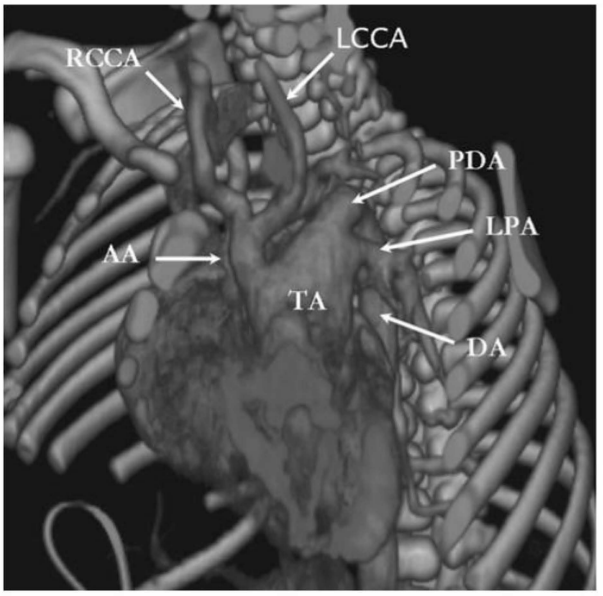



**FIGURE 79-13** Magnetic resonance imaging (MRI) in complex aortic arch interruption. Neonate with truncus arteriosus and interrupted aortic arch (type A). Truncus arteriosus (TA) giving rise to right and left (LPA) pulmonary arteries and in direct continuity with the descending aorta (DA) via a patent ductus arteriosus (PDA). The ascending aorta branched in right (RCCA), left (LCCA) common carotid and left subclavian arteries (LSCA). The right subclavian artery (not visible) originated from the proximal right pulmonary artery and was divided intraoperatively. (Courtesy of Philip J. Spevak, MD, Division of Pediatric Cardiology, the Johns Hopkins University.)

## Treatment

### MEDICAL MANAGEMENT

The introduction of $PGE_1$ in 1976 was revolutionary in the treatment of IAA. Reestablishment of ductal flow is an imperative first step in the initial management of this abnormality. Maximization of pulmonary resistance may also be beneficial in increasing systemic blood flow, improving end-organ perfusion and avoiding associated systemic acidosis. This can be achieved by minimizing administration of oxygen as well as employing a strategy of hypoventilation and permissive hypercapnea via specific ventilatory support. Metabolic acidosis should be treated. The achievement of appropriate volume status as well as the use of inotropic agents may also be critical in resuscitation. With medical management, the neonate can be stabilized and will ultimately be a more appropriate candidate for surgical intervention, markedly improving surgical outcomes.

### SURGICAL TECHNIQUES

Improvements in cardiopulmonary bypass technique as well as the use of selective antegrade or regional low-flow cerebral perfusion have changed operative strategies for the treatment of this disease entity. Single-stage repair with direct anastomosis with or without the need for circulatory arrest has become a strategy employed at most centers.[51,52] As an alternative, a staged approach with direct repair of the IAA and pulmonary artery banding for palliation of the VSD, followed by subsequent closure of the VSD, may be considered. Using this philosophy, a left thoracotomy is employed not only for cases of IAA without associated VSD but also in a staged approach for neonates with associated VSD. IAA represents a spectrum of entities; thus the surgical approach must take patient-specific factors into consideration.

In the case of type A IAA, the anatomic abnormality can be conceptually classified in the same category as coarctation. An extended end-to-end anastomosis via left thoracotomy and without the need for cardiopulmonary bypass may be the management of choice if no other intracardiac pathology is present. The choice of a single versus a staged approach for treatment of type B IAA with or without associated cardiac anomalies is more complex.

In neonates undergoing one-stage repair, it is very helpful to place an invasive arterial monitoring line in the right upper extremity. This allows perfusion pressures to be monitored and documented during periods of antegrade cerebral perfusion. Umbilical and/or femoral arterial pressure

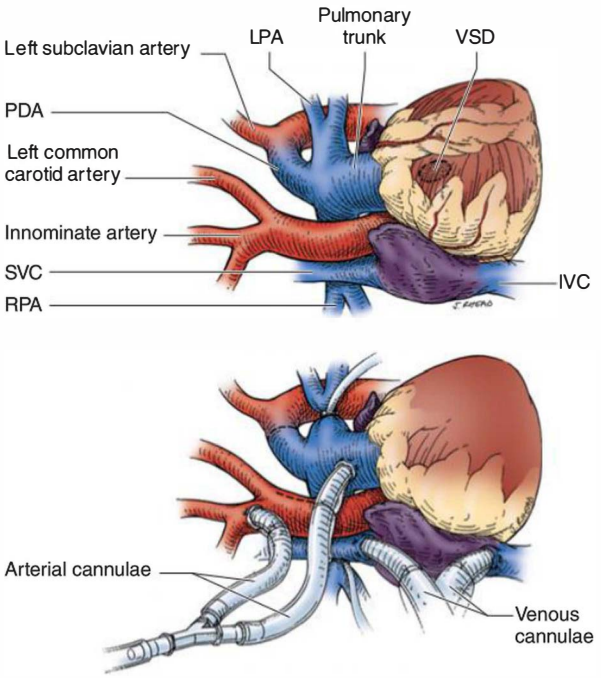



**FIGURE 79-14** Cardiopulmonary bypass (CPB) strategy for repair of type B interrupted aortic arch as schematically represented from the operating surgeon's perspective (top). The arterial return line is bifurcated and introduced into the main pulmonary artery and ascending aorta. The cannulation site for the latter is positioned opposite to the anticipated anastomosis (dotted line, bottom panel). Systemic venous drainage is provided by bicaval or single (in small neonates) venous cannulas. Pulmonary artery snares are tightened on initiation of CPB. IVC, inferior vena cava; LPA, left pulmonary artery; PDA, patent ductus arteriosus; RPA, right pulmonary artery; SVC, superior vena cava; VSD, ventricular septal defect. (From Kouchoukos NT, Blackstone EH, Doty DB, et al. (eds). Coarctation of the aorta and interrupted aortic arch. In: *Kirklin/Barratt-Boyes: Cardiac Surgery,* 3rd ed. Philadelphia: Churchill-Livingstone, 2003:1358. With permission.)

can also be monitored to document the adequacy of distal perfusion and postrepair gradients. Single or bicaval venous cannulation is employed for venous drainage. An arterial cannula circuit with a Y-connector split is used to perfuse both the aortic arch proximal to the obstruction as well as the descending aorta via cannulation of the pulmonary artery trunk and advancing it toward the patent ductus arteriosus (Fig. 79-14). Cannulation of the ascending aorta should be performed along its right lateral aspect or separately at the base of the innominate artery to keep the region of the aorta that will be incised for anastomosis to the distal aortic limb clear. Also, once cardiopulmonary bypass has been initiated, it is critical to snare tourniquets around the branch pulmonary arteries to limit pulmonary runoff and preserve distal perfusion via the ductus arteriosus into the descending aorta.

Cooling is initiated with a goal of profound hypothermia (16–18°C). During the cooling phase, the aorta and its branches are extensively mobilized to obtain a tension-free anastomosis. After achieving the desired cooling, the descending aortic perfusion cannula is removed. The distal aorta is subsequently clamped and all ductal tissue is ligated proximally and excised distally.

During arch reconstruction, cerebral and cardiac perfusion pressures should be maintained at approximately 50 mL/kg/min at 22°C if selective antegrade cerebral perfusion is utilized.[53] Flows may be further reduced if the patient is cooled more aggressively. Perfusion pressures can be monitored via a right upper extremity arterial monitoring line. A direct end-to-side aortic anastomosis is performed without tension between the distal aorta and an aortotomy in the proximal aortic limb. The incision is made along the left posterolateral aspect of the ascending aorta, and it is enlarged to approximate the lumen of the distal aortic limb. The anastomosis is initially completed, along the posterior aspect of the vertically oriented ascending aorta (Fig. 79-15). If necessary, patch augmentation of any associated regions of hypoplasia may be considered. In case of anomalous right subclavian artery takeoff, division of this structure may aid in the mobilization of the descending thoracic aorta and improve the likelihood of a tension-free anastomosis.

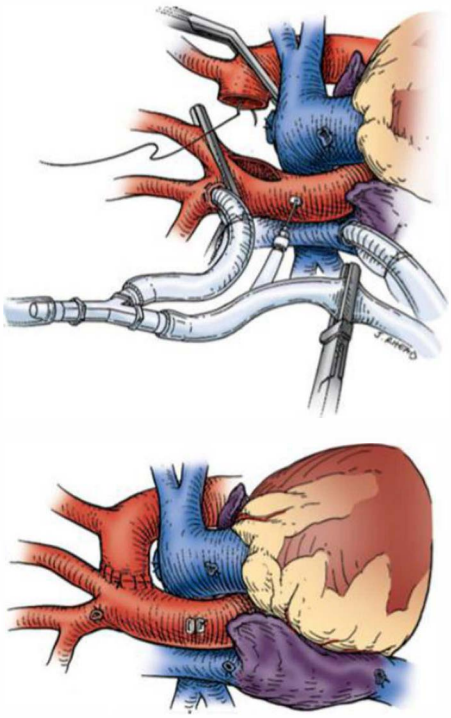


**FIGURE 79-15** End-to-side anastomosis between the ascending and descending aorta in type B aortic arch interruption. The return cannula in the pulmonary artery has been removed and selective antegrade cerebral perfusion is maintained (top). The end-to-side anastomosis is completed with a continuous polypropylene suture (bottom). (From Kouchoukos NT, Blackstone EH, Doty DB, et al. (eds). Coarctation of the aorta and interrupted aortic arch. In: *Kirklin/Barratt-Boyes: Cardiac Surgery,* 3rd ed. Philadelphia: Churchill-Livingstone, 2003:1358. With permission.)

While maintaining distal perfusion and after infusion of cold blood cardioplegia into the aortic root, the ascending aorta can be clamped and the VSD and/or other associated anomalies corrected. These can also be addressed during the initial cooling phase prior to aortic arch reconstruction. Issues related to LVOTO may be treated either via subaortic resection or, in extreme cases, by diverting left ventricular outflow through the VSD and pulmonary artery using an intracardiac baffle. The main pulmonary artery is then divided proximal to its bifurcation site and anastomosed to the side of the native aorta. Subsequently, a right ventricular outflow tract reconstruction is undertaken from the right ventricle to the confluence of the right and left pulmonary arteries.[54,55]

Alternatively, an intracardiac baffle is not performed and ventricular output is directed through both aorta and pulmonary artery [Damus–Kaye–Stansel (DKS) anastomosis] into the aortic arch. A modified Blalock–Taussig shunt is then performed to provide a source of pulmonary blood flow, deferring ventricular baffling and insertion of a right ventricle–pulmonary artery conduit to a later time.

Alternative approaches to the repair of IAA exist and should remain in consideration due to the broad disease spectrum that this entity represents. At the Indiana University School of Medicine–Riley Hospital for Children, a staged approach with the use of a left carotid artery swing-down technique has yielded excellent results. In this technique, via a left fourth interspace thoracotomy, patients underwent division of the left carotid artery with anastomosis of the divided end to the descending aorta (Fig. 79-16). Pulmonary artery banding was employed in cases with associated VSD. Although this strategy has the disadvantage of being a staged palliative approach, outcome data are quite favorable, especially with respect to early mortality. This strategy may be attractive in cases presenting other complex cardiac anomalies or other significant comorbidities such as very low birth weight.[56]

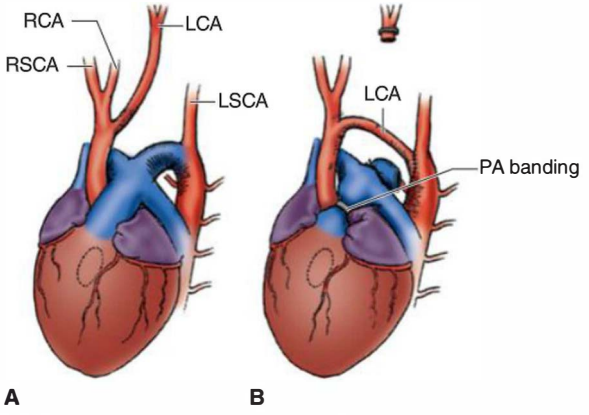



**FIGURE 79-16** Left common carotid (LCA) "turndown" repair of type B (left) aortic arch interruption. The artery is divided distally and anastomosed in an end-to-side fashion to the descending aorta (right). The ventricular septal defect (VSD) is left open and the pulmonary trunk is banded. Ao, aorta; LCA, left carotid artery; LSCA, left subclavian artery; RCA, right carotid artery; RSCA, right subclavian artery. (From Brown JW, Ruzmetov M, Okada Y, et al. Outcomes in patients with interrupted aortic arch and associated anomalies: A 20 year experience. *Eur J Cardiothorac Surg* 2006. In press. With permission.)

Postoperative care of patients with complete repair of a simple IAA should be relatively straightforward. Need for prolonged inotropic support or additional critical care monitoring should prompt a search for additional untreated hemodynamic lesions or uncorrected pathology. An undiagnosed or residual VSD may be identified by analyzing oxygen saturation data from a pulmonary artery line. Echocardiography may also be utilized. In unusual circumstances, cardiac catheterization may yield important data in regard to residual LVOTO.[48]

## Outcomes

Hospital mortality for neonatal single-stage repair of IAA in the current era is less than 10 percent.[46] This figure is unchanged by the presence of an associated VSD. Among subtypes of IAA, mortality has been described to be as low as 4 percent for type A interruption and 11 percent for type B. The highest survival is in the subgroup of patients with isolated type A IAA amenable to complete repair via left thoracotomy. Lowest survival data are published for patients with type C IAA. The presence of coexisting anomalies and the location of interruption have been shown to affect mortality risk. Other risk factors for mortality include preoperative clinical status with regard to degree and adequacy of resuscitation in addition to the presence and severity of LVOTO.[51] Following initial complete intracardiac repair, 5-year survival as high as 70 percent has been documented.[57] The most extensive reported long-term follow-up has been to 16 years and has described an overall survival of 59 percent, with a need for arch reintervention of 28 percent.[58] As additional long-term data become available, these figures will likely improve as a reflection of advances in medical and surgical therapy.

In the Indiana University School of Medicine experience using a staged approach and left carotid swing-down for arch reconstruction, operative mortality for patients with IAA and VSD, regardless of interruption subtype, was 0.3 percent (1 of 44); 27 percent of these patients had associated LVOTO. In patients with more complex associated anomalies, such as Taussig–Bing double-outlet right ventricle or truncus arteriosus, there was no mortality for staged intervention using left carotid swing-down.[56]

Morbidity issues for IAA are somewhat specific to subtype as well as anatomic variations. Left recurrent laryngeal and phrenic nerve injuries may occur owing to the extensive dissection required around the aortic arch and adjacent structures. The left mainstem bronchus passes under the arch of the aorta; as a result, anastomotic tension between the proximal and distal aortic limbs may induce a bowstring effect over the bronchus, yielding airway obstruction and associated pulmonary obstructive issues.

Late morbidity can be divided into two primary categories: persistence of a transaortic gradient or worsening

LVOTO. Pressure gradients across the anastomosis are more likely to occur in situations where synthetic patch material has been employed, owing to a lack of growth potential. The use of autologous tissue is preferable. Patients with a direct arch anastomosis have as high as a 60 percent incidence of late obstruction (gradient greater than 30 mm Hg) within 18 months of surgery.[46] Percutaneous balloon dilatation can safely relieve residual or recurrent arch obstruction in the majority of these patients. In more recent series, however, freedom from reintervention due to gradients across the reconstruction is excellent, reported at 86 percent at 3 years.[53] A more problematic long-term detrimental outcome is late subaortic obstruction or LVOTO. Freedom from reintervention for such pathology has been reported as high as 77 percent at 3 years.[57]

## Conclusions

IAA represents an extreme, life-threatening form of congenital heart disease; it is a lesion that may be treated by several approaches. In the current era, surgical repair yields excellent outcomes. The presenting clinical picture and effective medical stabilization plays a major role in overall outcome. In most centers, single-stage repair is now the preferred operative approach. However, a two-stage approach, with initial arch reconstruction using a left carotid artery swing-down and pulmonary artery banding with subsequent intracardiac repair, yields excellent results and may be considered in selected cases. Early outcomes are dependent on preoperative medical management, subtype of interruption, and extent of associated anomalies. Long-term outcomes are associated with levels of transaortic reconstruction, pressure gradients as well as issues of LVOTO.

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## COARCTATION OF THE AORTA AND INTERRUPTED AORTIC ARCH BOARD REVIEW QUESTIONS (CHAPTER 79)

1. Which is not associated with CoA?
   A. VSD
   B. Bicuspid aortic valve
   C. Partial atrioventricular septal defect
   D. Taussig–Bing anomaly
   E. Shone complex

2. Which is correct regarding catheter-based interventions for coarctation?
   A. Nearly 60 percent of neonates undergoing balloon angioplasty will require subsequent surgical repair.
   B. Up to 25 percent of neonates will develop saccular aneurysms after balloon angioplasty.
   C. Less than 5 percent of neonates will develop recoarctation after surgical repair.
   D. Balloon angioplasty has about a 50 percent success rate for relieving the gradient for recurrent coarctation.
   E. There is a 5 percent incidence of restenosis after balloon angioplasty for recurrent coarctation.

3. Which is correct regarding postoperative complications after repair of coarctation?
   A. Arterial hypertension is uncommon.
   B. Postcoarctectomy syndrome occurs in 5 to 10 percent.
   C. Paraplegia occurs in 2 percent of patients.
   D. Division of arterial collaterals is not a risk factor for paraplegia.
   E. Neonatal repair has an operative mortality of 3 percent.

4. Which is not associated with IAA?
   A. Microdeletion of q11 segment of chromosome 22
   B. VSD
   C. Aberrant right subclavian artery
   D. Subpulmonary stenosis
   E. Bicuspid aortic valve

5. Which is correct regarding outcomes after repair of IAA?
   A. Hospital mortality is about 15 percent.
   B. Coexistent anomalies have little effect on risk.
   C. Five-year survival is about 70 percent.
   D. Patients with a direct arch anastomosis have a low incidence of late obstruction.
   E. Subaortic obstruction occurs in nearly 75 percent of patients at 3 years.

## ANSWERS

1. **Answer: C.** Partial AV septal defects are not typically associated with CoA. VSD, bicuspid aortic valve, Taussig–Bing anomaly, and Shone complex are all associated with coarctation.
2. **Answer: A.** Nearly 60 percent of neonates undergoing balloon angioplasty will require subsequent surgical repair. Less than 15 percent of neonates will develop saccular aneurysms after balloon angioplasty. Nearly 20 percent of neonates will develop recurrent coarctation after surgical repair. There is a 90 percent success rate for balloon angioplasty in these patients in relieving the gradient, and about 15 percent will require reintervention.

3. **Answer: B.** Postcoarctectomy syndrome (abdominal discomfort) occurs in 5 to 10 percent of patients for a few days after surgery. Arterial hypertension is common despite adequate repair. Paraplegia occurs in less than 1 percent of patients and has been associated with division of arterial collaterals. Neonatal repair has an operative mortality of less than 2 percent.
4. **Answer: D.** Subaortic, not subpulmonary, stenosis is associated with IAA. As with CoA, VSD and bicuspid aortic valve are common associations. Anomalies of the great vessels are relatively common. Type B interrupted arch is associated with DiGeorge syndrome and 22q11 microdeletions.
5. **Answer: C.** Five-year survival is about 70 percent. Hospital mortality is less than 10 percent in most series. Coexistent anomalies have a significant impact on operative risk. Patients with a direct arch anastomosis have an incidence of late obstruction approaching 60 percent. Subaortic obstruction is less common and occurs in about 25 percent of patients at 3 years.

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# 80 Cor Triatriatum

*Giancarlo Crupi*

**KEY CONCEPTS**

- Epidemiology
  - Cor triatriatum is an uncommon congenital cardiac anomaly in which either the left (cor triatriatum sinister) or right (cor triatriatum dexter) atrium is divided into two chambers by a membrane. Subdivided left atrium represents the most frequent anatomic variant of this lesion, and accounts from 0.1 to 0.4 percent of all congenital heart defects.
- Morphology
  - The pulmonary veins enter a proximal chamber (common pulmonary venous chamber) separated by a fibromuscular membrane from a distal chamber where the left atrial appendage and the mitral valve are found. The proximal and distal chambers may communicate through one or more openings within the dividing membrane, and an atrial septal defect (ASD) is usually present.
- Pathophysiology
  - In the absence of associated cardiac lesions, the pathophysiology of subdivided left atrium depends on the resulting obstruction to pulmonary blood flow. Pulmonary overcirculation is present when left-to-right shunting occurs through an ASD between common pulmonary venous chamber and right atrium.
- Clinical features
  - The clinical presentation in infancy is similar to that of total anomalous pulmonary venous connection, with low cardiac output, pallor, tachypnea, poor peripheral pulses, and failure to thrive. Death may occur within the first year of life in 75 percent of untreated patients with significant obstruction. Children and young adults present with signs of pulmonary venous hypertension of various importance.
- Diagnosis
  - Diagnosis is usually established by transthoracic and transesophageal echocardiography, although magnetic resonance imaging (MRI) can be used in selected cases. Cardiac catheterization may be indicated in the presence of associated cardiac lesions.
- Treatment
  - Resection of the membrane through a right atrial approach is recommended in infants, whereas a left atrial approach through the common pulmonary venous chamber may be used in older children and adults and in the presence of associated anomalies. Percutaneous catheter disruption of the membrane may represent an alternative to surgery in selected cases of subdivided right atrium. Outcomes are dependent on the preoperative clinical condition.

## DEFINITION

The classic definition of cor triatriatum is based on the recognition that either the left atrium (cor triatriatum sinister) or the right atrium (cor triatriatum dexter) is divided into two chambers by an abnormal fibromuscular membrane. The terms *subdivided left* or *right atrium*[1-4] will be used throughout this chapter, highlighting in a more comprehensible fashion the basic anomaly of this uncommon cardiac malformation.

In the commonest left-sided variant of this lesion, the pulmonary veins enter a proximal common pulmonary venous chamber, which is separated by a fibromuscular membrane from a distal chamber containing the mitral valve and left atrial appendage.

Subdivided right atrium is a much rarer anomaly in which a membrane, originating from the crista terminalis, divides the trabecular portion of the right atrium from the venae cavae. This entity should be distinguished[5] from the more common occurrence of prominent eustachian or thebesian valves.

## HISTORICAL BACKGROUND

The typical findings of subdivided left atrium were first described in 1868 by Church,[6] although the term *cor triatriatum* was initially applied to this anomaly by Borst in 1905.[7]

Subdivided left atrium was first diagnosed with angiography by Miller in 1964[8] and with echocardiography by Ostman-Smith in 1984.[9] Surgical repair was first accomplished in 1956.[10,11] Cor triatriatum dexter was described by Rokitanski in 1875,[12] yet noninvasive diagnosis by means of echocardiography has been increasingly reported only since 1987.[13] Successful surgical repair of subdivided right atrium was first reported in 1972.[14,15]

## BASIC EMBRYOLOGY

The morphogenesis of subdivided left atrium remains unclear, and the various hypotheses reported thus far[5] fail to explain all the anatomic variants of this anomaly. The entrapment theory proposed by Van Praagh and Corsini[16] is consistent with the findings observed in most cases of subdivided left atrium as well as with the hourglass and the tubular types described by Marin-Garcia and colleagues,[17] where no membrane is seen to divide the common pulmonary venous chamber from the mitral valve and the left atrial appendage. The entrapment theory postulates that subdivided left atrium results from the entrapment of the left atrial ostium of the common pulmonary vein by tissue of the right horn of the sinus venosus, leading to failure in the incorporation of the common pulmonary veins into the left atrium during the fifth week of embryonic development. Consequently, these authors use the term *common pulmonary vein chamber* to describe the proximal chamber, which receives the pulmonary veins. The entrapment theory fails, however, to explain the coexistence of subdivided left atrium with either total or partial anomalous pulmonary venous drainage.[4]

The morphogenesis of subdivided right atrium is less controversial.[3–5] During early cardiac development, the opening of the sinus venosus in the right portion of the common atrium is delineated by two valves, which join superiorly to form the septum spurium. The left valve becomes incorporated in the septum secundum, whereas the superior portion of right valve (which regresses at around 12 weeks of gestation) forms the crista terminalis; the remnants of the inferior portion form the eustachian and thebesian valves. According to Gharagozloo,[5] the obstructing membrane in subdivided right atrium originates from the crista terminalis and should be distinguished from the more commonly observed prominent eustachian or thebesian valves. In essence, subdivided right atrium is caused by the persistence of an unusually prominent right valve of the sinus venosus.

## MORPHOLOGY

The most comprehensive classification of the anatomic variants of subdivided left atrium was reported by Krabill and Lucas.[18] In its classic form (Fig. 80-1), the right and left pulmonary veins enter a common pulmonary venous chamber (proximal chamber), which is, in most instances,

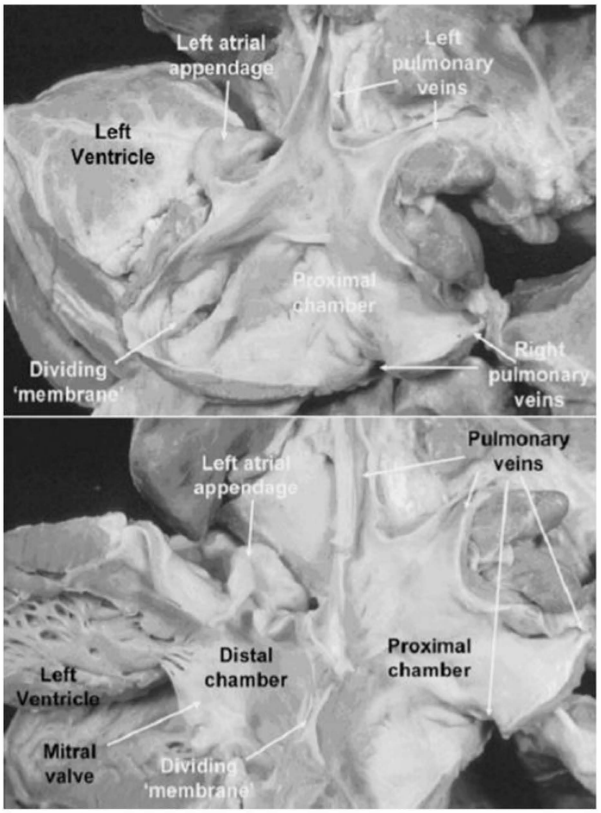



**FIGURE 80-1** Autopsy specimen of subdivided left atrium. Top: The common pulmonary venous chamber (proximal chamber) is opened to show the drainage of the left and right pulmonary veins and the dividing membrane with a fenestration in its center. Bottom: The distal chamber and the left ventricle are opened to show the membrane separating the proximal from the distal chamber, where the mitral valve and the left atrial appendage are seen. (Courtesy of Professor RH Anderson, Institute of Genetic Medicine, Newcastle University.)

separated by a fibromuscular diaphragm from a distal chamber where the mitral valve and the left atrial appendage are found. The dividing membrane may show a single orifice ranging in diameter between less than 3 mm to about 1 cm; occasionally, several small defects might be seen. In two unusual variants of subdivided left atrium (the so-called hourglass and tubular types), no membrane is found to divide the left atrium (Fig. 80-2).[16] In these variants, the thicker-walled common pulmonary vein chamber is usually posterior and somewhat superomedial to the thin-walled proximal chamber. Associated anomalies may be present in more than 50 percent of patients with this lesion. In addition to the more frequent finding of partial and total anomalous pulmonary venous connection, associated anomalies include ventricular septal defect (VSD), atrioventricular septal defect (AVSD or AV canal), tetralogy of Fallot, and coarctation of the aorta. A left superior vena cava[19] is found more frequently than in other types of congenital heart defects and may be associated with a partially or totally unroofed coronary sinus.[20]

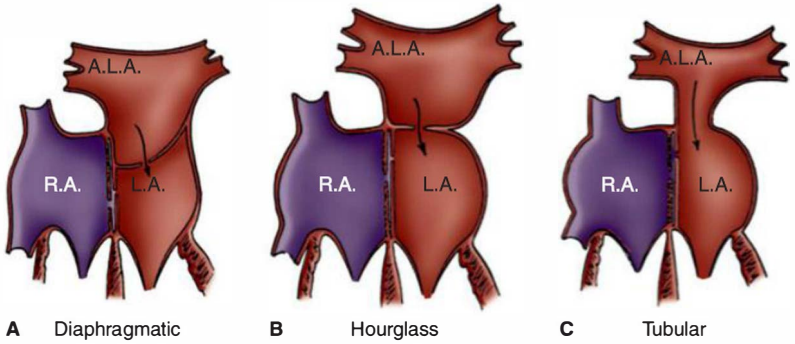



**FIGURE 80-2** Anatomic types of cor triatriatum (subdivided left atrium). **Type A** is the commonest anatomic variant: a fibromuscular membrane divides the accessory left atrial chamber (ALA, representing the common pulmonary venous chamber) from the true left atrium (LA, or distal chamber) where the mitral valve and the left atrial appendage are found. In **type B**, described as the *hourglass type*, a constriction is seen externally at the junction between the common pulmonary venous and distal chambers, where no membrane is found. No dividing membrane can also be found in **type C** (*tubular type*), where a tubular channel receives all the pulmonary veins (common pulmonary venous chamber) and joins the distal chamber. RA, right atrium. (From Marin-Garcia J, Tandon R, Lucas RV Jr, et al. Cor triatriatum: Study of 20 cases. *Am J Cardiol* 1975;35:59. With permission.)

The typical finding of subdivided right atrium is the presence of a membrane separating the right atrial appendage and the tricuspid orifice from the venae cavae and the coronary sinus. The term *subdivided right atrium* should be reserved for those hearts where the dividing membrane originates from the crista terminalis (Fig. 80-3) and, as mentioned above, this entity should be distinguished from those cases of unusual prominence of either the eustachian or thebesian valves, which do not originate from the crista terminalis.[3,5] Yet the former lesion has often been described at necropsy, whereas the latter anatomic variant has been increasingly diagnosed clinically by echocardiography. The most commonly observed cardiac malformations associated with subdivided right atrium include pulmonary valve stenosis or atresia, hypoplastic right ventricle, and tricuspid valve stenosis or atresia.[21,22]

## PATHOPHYSIOLOGY

Obstruction of pulmonary venous return to the left atrium is the key hemodynamic feature of subdivided left atrium. The severity of obstruction is multifactorial and depends not only on the size of the fenestration in the dividing membrane but also on both the presence and size of an ASD between the chamber of the common pulmonary veins and the right atrium, as well as on associated cardiac lesions. Severe pulmonary venous hypertension, indistinguishable from that observed in obstructed total anomalous pulmonary venous connection, is present when the size of the fenestration is severely restrictive (3 mm or less) and the atrial septum is intact. Conversely, when a large ASD is present between the common pulmonary venous chamber and the right atrium or in presence of either a partial or a total unobstructed pulmonary venous return, left-to-right shunting will be present and pulmonary venous obstruction may not be obvious.

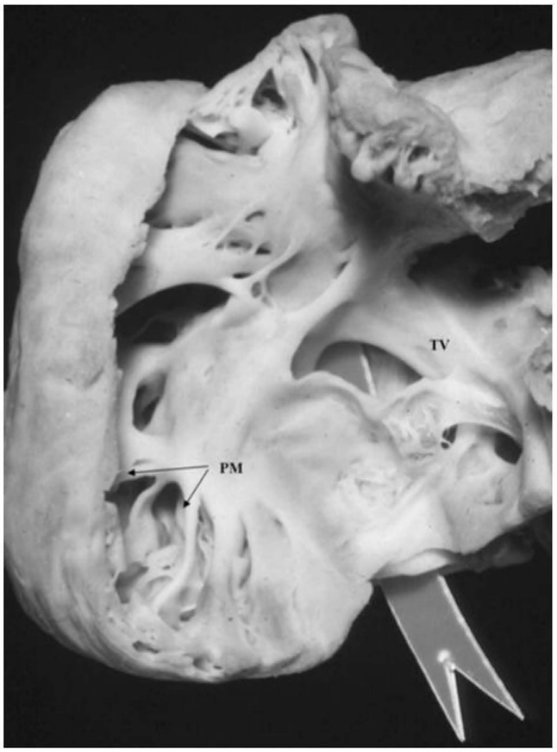



**FIGURE 80-3** Autopsy specimen of subdivided right atrium due to persistence of the right venous valve. The right atrium and the right ventricle are opened to show a large fibrous membrane originating from the crista terminalis and dividing the right atrial appendage and the tricuspid valve from the venae cavae. The membrane deflects blood from the inferior vena cava (through which an arrow is placed) into the left atrium via the fossa ovalis. The opening of the superior vena cava is also behind the venous valve and is not visible. The vestibule of the tricuspid valve is seen to the right lower corner of the figure. PM, pectinates muscles; TV, tricuspid valve. (Courtesy of Professor RH Anderson, Institute of Genetic Medicine, Newcastle University.)

The hemodynamic features of subdivided right atrium are equally based on the severity of obstruction to systemic venous return and on the presence of an ASD. Cyanosis may in fact be frequent due to shunting of inferior caval blood into the left atrium through an ASD. Right-sided congestive heart failure with elevated central venous pressure may be present in cases with intact atrial septum and right ventricular inflow or outflow obstruction.

## CLINICAL FEATURES

The clinical presentation of patients with subdivided left atrium but without major associated lesions will depend on the degree of obstruction to pulmonary blood flow through the dividing membrane. If the communication between the common pulmonary venous chamber and the mitral valve is small (3 mm or less), the patient may become symptomatic in the first few months of life as a consequence of ongoing low cardiac output with pallor, poor peripheral pulses, tachypnea, and growth failure. In the presence of associated anomalous pulmonary venous return or when an ASD is present between the common pulmonary venous chamber and the right atrium, symptoms due to increased pulmonary blood flow (such as recurrent respiratory infections, congestive heart failure, and failure to thrive) may coexist.[23]

The severity and quality of symptoms in patients with subdivided right atrium also seem to depend largely on two variables: the degree of obstruction produced by the membrane and the state of the interatrial septum. With only a minor degree of obstruction, this lesion is often asymptomatic and may be detected only incidentally at surgery for correction of other cardiac anomalies or during echocardiography. Cyanosis due to shunting of the inferior caval blood in the left atrium through an ASD is the dominant clinical feature when the membrane is severely obstructive. This situation is often well tolerated into adult life, and rarely results in severe hypoxemia in infancy. Right-sided heart failure with elevated central venous pressure due to obstruction of the tricuspid valve or the right ventricular outflow tract may occur when the atrial septum is intact.[24]

## DIAGNOSTIC MODALITIES

Echocardiography is the method of choice for identification of both subdivided left and right atrium.[25,26] Two-dimensional transthoracic echocardiography (Fig. 80-4) may be supplemented by transesophageal imaging (Fig. 80-5) for further evaluation.[27] The use of magnetic resonance imaging (MRI) has been increasingly reported in recent literature for diagnosis and preoperative planning. MRI is thought to have a higher sensitivity than echocardiography and angiography.[28] In general, MRI provides better spatial resolution and superior tissue contrast when compared with

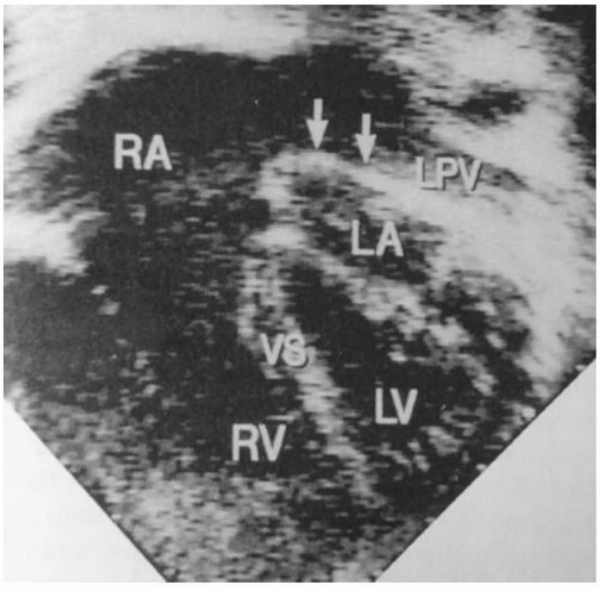



**FIGURE 80-4** Transthoracic echocardiographic imaging (apical four-chamber view) of subdivided left atrium. The common pulmonary venous chamber communicates via a large atrial septal defect with the right atrium and is separated by a membrane (arrow) from the left atrium (distal chamber). LA, left atrium; LV, left ventricle; RA, right atrium; RN, right ventricle; VS, ventricular septum. (From Van Son JA, Autschback R, Mohr FW. Repair of cor triatriatum with partially unroofed coronary sinus. *Ann Thorac Surg* 1999;68:1414. With permission.)

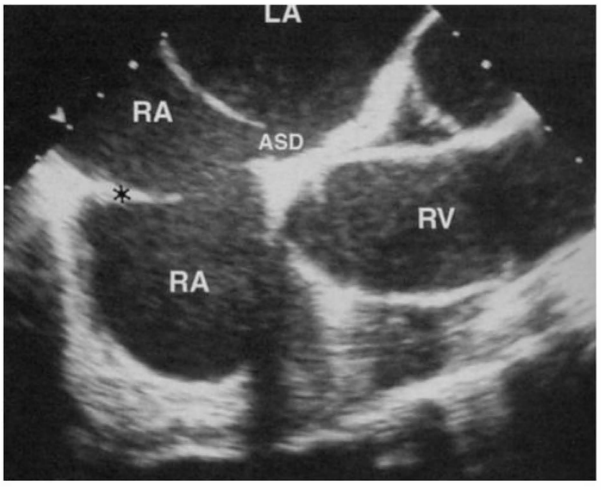



**FIGURE 80-5** Transesophageal echocardiographic imaging of subdivided right atrium. Long-axis view demonstrates the dividing membrane (*) in the right atrium. ASD, atrial septal defect; LA, left atrium; RA, right atrium; RV, right ventricle. (From Joe BN, Poustchi-Amin M, Wooddard PK. Cor triatriatum dexter. *Radiology* 2003;226:702. With permission.)

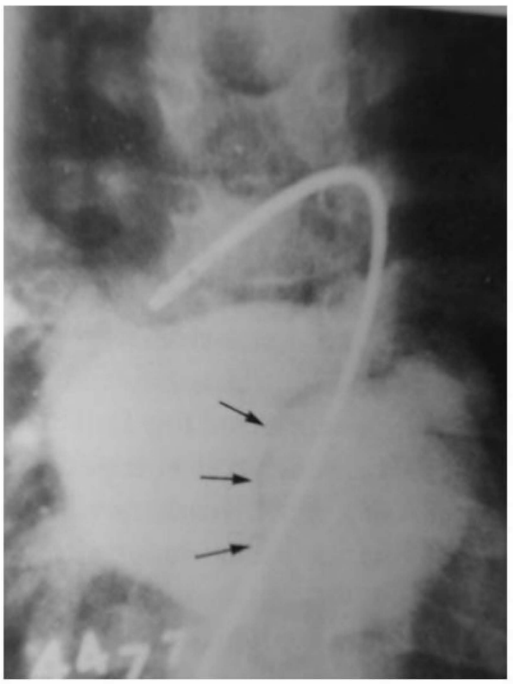


**FIGURE 80-6** Angiographic imaging of subdivided left atrium. Pulmonary artery injection of contrast medium delineates the dividing membrane (arrowed) between the common pulmonary venous chamber and the distal chamber, where the left atrial appendage is seen. The atrial septum was intact. (From Arciniegas E, Farooki ZQ, Hakimi M, et al. Surgical treatment of cor triatriatum. *Ann Thorac Surg* 1981;32:571. With permission.)

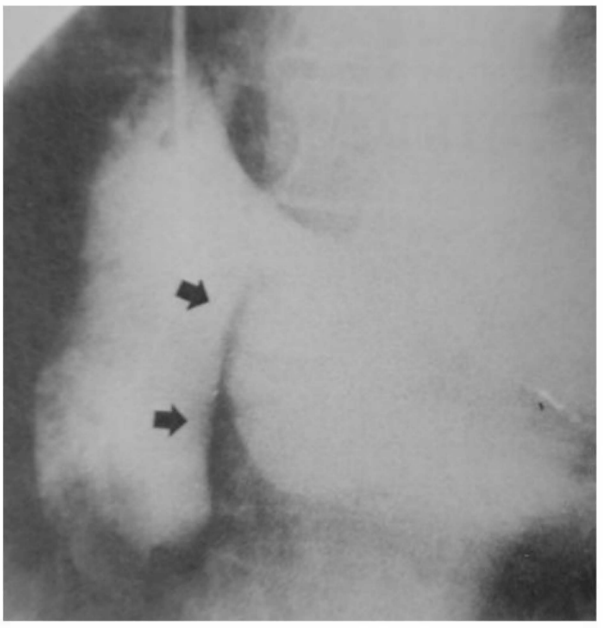


**FIGURE 80-7** Angiographic imaging of subdivided right atrium. Superior vena cava injection of contrast medium demonstrates the division of the right atrium by an abnormal remnant (arrowed) of the right valve of the sinus venosus. (From Ott DA, Cooley DA, Angelini P, et al. Successful surgical correction of symptomatic cor triatriatum dexter. *J Thorac Cardiovasc Surg* 1979;78:573. With permission.)

echocardiography. Cardiac catheterization and angiography (Figs. 80-6 and 80-7) are no longer indicated for the diagnosis of subdivided atrium unless major associated cardiac lesions are suspected.

## SURGICAL MANAGEMENT

Surgery is the only mode of treatment for symptomatic patients with subdivided left atrium. Timing of operation is based primarily on the clinical status, and prompt surgery is indicated for those infants who present with symptoms of severely obstructed pulmonary blood flow. Without surgical treatment, 75 percent of patients born with a significant degree of obstruction die in infancy.[29] Urgent repair is also indicated in older patients presenting with chronic symptoms. Planning of the operation is based on the coexistence and the complexity of associated lesions. Before operation, the drainage of all pulmonary and systemic veins should be ascertained. In the presence of a left superior vena cava (frequently associated with subdivided left atrium), the possibility that the coronary sinus may be partially or totally unroofed should be ruled out.

Moderately hypothermic or normothermic cardiopulmonary bypass with bicaval cannulation and antegrade cold blood cardioplegia may be routinely used in straightforward cases. The strategy of normothermic versus hypothermic cardiopulmonary bypass remains controversial[30–32]; hypothermic circulatory arrest should be used only in the presence of complex associated lesions.[33]

A right atrial approach (Fig. 80-8) is recommended for infants and small children, especially in the presence of an enlarged common pulmonary venous chamber. After aortic cross-clamping, the right atrium is opened through a longitudinal incision parallel to the atrioventricular groove. A longitudinal septal incision is carried out through the fossa ovalis, obtaining optimal exposure of the fibromuscular membrane and of the mitral valve below it. The membrane can be excised completely while preserving the integrity of the mitral valve. The atrial septum is reconstructed with a pericardial patch.

A longitudinal incision in the common pulmonary vein chamber just posterior to the interatrial groove (Fig. 80-9) can be satisfactorily used in older children and adults. Anterior retraction of the atrial septum allows adequate exposure of the membrane for subsequent resection. A potential pitfall of this approach is the initial difficulty of assessing the relationship between the membrane and the mitral valve below it. Closure of the fossa ovalis or patch reconstruction of the atrial septum may be more technically demanding with this approach. Modified ultrafiltration and the use of nitric oxide in infants with severe

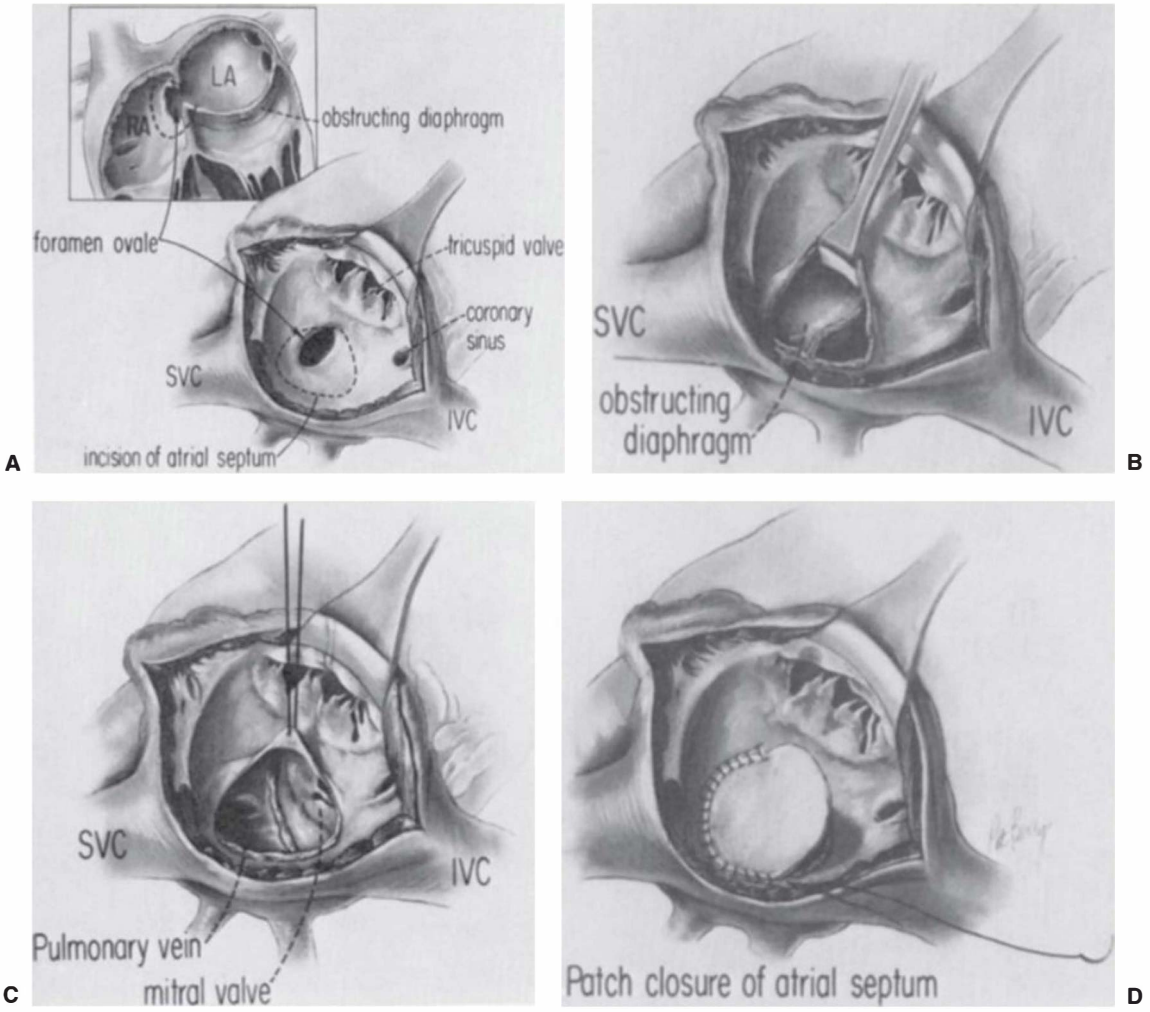



**FIGURE 80-8** Right atrial approach for repair of subdivided left atrium. **A.** Right atrial incision through the superior and inferior margins of the foramen ovale. **B.** These incisions are carried to the right atrial wall, providing simultaneous exposure of both the common pulmonary venous chamber and the distal chamber. This allows careful evaluation of the relationship between the dividing membrane and the mitral valve. **C.** Complete excision of the membrane brings the pulmonary veins and the mitral valve in continuity. **D.** Reconstruction of the septal incision with a pericardial patch. IVC, inferior vena cava; SVC, superior vena cava. (From Richardson JV, Doty DB, Siewers RD, et al. Cor triatriatum (subdivided left atrium). *J Thorac Cardiovasc Surg* 1981;81:232. With permission.)

pulmonary hypertension can be a very useful therapeutic adjunct in the early postoperative phase.

Resection of the obstructing membrane is the treatment of choice in patients with subdivided right atrium, although percutaneous catheter disruption of the membrane[34] may represent an alternative to surgery in selected cases without associated lesions. Transesophageal echocardiography may be useful for a better definition of the relationship of the membrane with the surroundings structures. Normothermic cardiopulmonary bypass on a beating heart with bicaval cannulation may be used in simple cases of subdivided right atrium without septal defects. The surgical approach in the presence of associated anomalies should be tailored to the individual case.

## OUTCOMES

Aside from the description of occasional individual cases,[20,35] there are only a few reports in the literature of relatively large cohorts of patients with cor triatriatum.[23,36] Most of the literature regarding this topic was published in earlier decades,[2,19,37,38] making any comparison with modern practice in the surgical management of infants and small children not entirely meaningful. Regardless of the time of publication, it is not surprising that most reported deaths occurred within the first year of life in infants who were severely symptomatic, or in the presence of complex associated lesions. In high-risk cases, hospital mortality has been reported between 33 and 60 percent.[23,37] These results underscore the importance of an

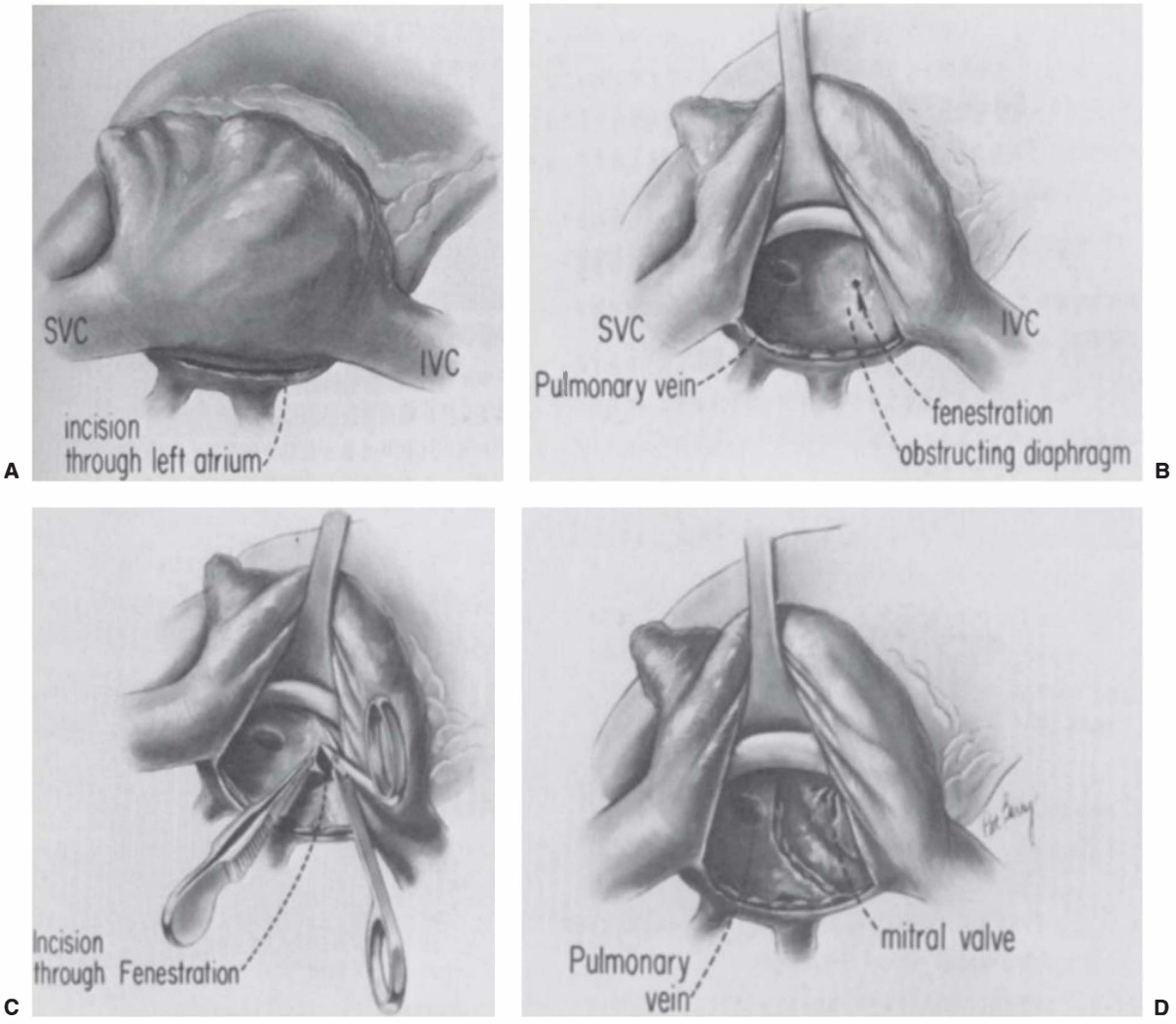



**FIGURE 80-9** Left atrial approach for repair of subdivided left atrium. **A.** A longitudinal incision is made in the left atrium (common pulmonary venous chamber) posterior to the interatrial groove. **B.** The atrial septum is retracted superiorly, exposing the dividing membrane with central fenestration. **C.** Excision of the dividing membrane is commenced by opening the fenestration and continued leftward after visualization of the left inferior pulmonary vein and of the mitral valve. **D.** The pulmonary veins are seen in continuity with the mitral valve. LA, left atrium (common pulmonary venous chamber); RA, right atrium; SVC, superior vena cava; IVC, inferior vena cava. (From Richardson JV, Doty DB, Siewers RD, et al. Cor triatriatum (subdivided left atrium). *J Thorac Cardiovasc Surg* 1981;81:232. With permission.)

early and detailed preoperative diagnosis, particularly when complex lesions are associated. In contrast, hospital mortality is uncommon after repair of this lesion in older patients.

Unfavorable late events leading to restenosis—such as pulmonary vein stenosis[2] and incomplete resection of the dividing membrane between the common pulmonary venous and the distal chamber—are exceedingly rare.[39]

The life expectancy of patients with subdivided left atrium without major associated cardiac lesions approaches that of the general population, particularly if repair is performed in infancy.

With the exception of the reports by Hansing and coworkers[14] and Trento and associates,[3] most descriptions of the surgical management of patients with subdivided right atrium have been single case reports.[15,40] This may represent the primary lesion, and successful surgical treatment has been reported even in the first few months of life.[3,15] On the other hand, an obstructing membrane within the right atrium may be found at operation associated with other lesions causing obstruction to pulmonary blood flow, and treatment and prognosis depends on that of the dominant lesion.

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## COR TRIATRIATUM BOARD REVIEW QUESTIONS (CHAPTER 80)

1. Which is not associated with subdivided left atrium?

   A. VSD
   B. Partial atrioventricular septal defect
   C. Tetralogy of Fallot
   D. Left superior vena cava
   E. Pulmonary stenosis

2. Which is true regarding surgical management of subdivided atrium?

   A. Fifty percent of patients born with subdivided left atrium die in infancy without treatment.
   B. Urgent repair is indicated in older patients with chronic symptoms.
   C. Hypothermic circulatory arrest is used in all patients with subdivided left atrium.
   D. A left atrial approach is recommended for repair of subdivided left atrium in infants.
   E. Percutaneous disruption of the obstructive membrane is the preferred approach in patients with subdivided right atrium.

3. Which is correct regarding pathophysiology of subdivided atrium?

   A. Severe pulmonary hypertension occurs when the fenestration is small and the atrial septum is open.
   B. A large ASD increases pulmonary hypertension due to left-to-right shunting.

C. Cyanosis is frequent due to preferential shunting from the IVC through an ASD.
D. Elevated central venous pressures can occur with a large ASD and RVOT obstruction.
E. Obstruction of pulmonary arterial outflow is the key hemodynamic feature.

## ANSWERS

1. **Answer: E.** Pulmonary stenosis is not associated with subdivided left atrium. VSD, AV canal defects, tetralogy of Fallot, coarctation of the aorta, and left superior vena cava are all associated with this defect.
2. **Answer: B.** Urgent repair is indicated in an older patient with subdivided left atrium that presents with chronic symptoms. Up to 75 percent of patients with severe obstruction will die without treatment during infancy. Hypothermic circulatory arrest is typically only used when there are associated complex anomalies. A right atrial approach is recommended for repair of subdivided left atrium in infants. Surgical repair remains the preferred approach for patients with subdivided right atrium.
3. **Answer: C.** Cyanosis is frequent due to preferential shunting from the IVC through an ASD. Severe pulmonary hypertension occurs when the fenestration is small and the atrial septum is intact. A large ASD relieves pulmonary hypertension due to left-to-right shunting. Elevated central venous pressures can occur with an intact atrial septum and RVOT obstruction. Obstruction of pulmonary venous return is the key hemodynamic feature.

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# 81 Valvular Disease in Children

*Christian P. Brizard*
*Yves d'Udekem d'Acoz*

## MITRAL VALVE DISEASE IN CHILDREN

### Anatomy and Embryology

#### ANATOMY

Precise knowledge of the normal anatomy of the mitral valve and the interpretation of echocardiographic studies is essential to understanding the mechanism of mitral valve regurgitation or stenosis (functional classification), elucidate the location of leaflet dysfunction (segmental valve analysis), and plan and achieve successful surgical repair. The anatomy of the normal mitral valve in the child does not differ from that in the adult.[1]

#### EMBRYOLOGY

The embryology of the mitral valve is complex. Our understanding of the formation of the leaflets and suspension apparatus has evolved, so that the current approach is mainly based on immunohistochemistry, in vivo labeling of cushion tissue, and scanning electron micrography of human and avian embryos.[2,3] In humans, the mitral valve develops between the 5th and 15th weeks of embryonic life. During the fifth week, the atrioventricular canal is defined and lined with two cushions mostly toward the left side of the canal. The anterior leaflet of the mitral valve derives from the junction of the superior and inferior cushions, whereas the posterior leaflet derives from an infolding of the atrioventricular–muscular wall and the development of a lateral cushion. The wedging of the aortic root into the superior bridging leaflet (mostly originating from the superior cushion) will separate the developing mitral valve from its septal attachments and create the aortomitral continuity.[4] The process required for the transformation of the endocardial cushion into valvar tissue is poorly understood. The presence of calcineurin and periostin is required. As the cushion tissue elongates and grows toward the ventricular cavity, it is gradually delaminated from the underlying myocardium and the leaflet becomes progressively shaped as a funnel-like structure totally attached to the myocardium. Perforations then appear into the valve leaflet and grow to form the chordae tendineae. The atrial aspect of the cushion will generate the spongy atrial layer and the ventricular layer will generate the fibrous part of the mitral valve and chordal apparatus. The separation between atrial and ventricular myocardium is dependent on the sulcus tissue located on the epicardial side of the junction. The development of the papillary muscles takes place simultaneously, originating from the myocardium. A horseshoe-shaped ridge lies within the left ventricle. The anterior and posterior parts of this ridge lose contact with the ventricular wall, forming the papillary muscles and increasing in size, while maintaining structural continuity with the cushion tissue at the tip of the papillary muscle. The midportion of the muscular ridge will be incorporated into the apical trabeculations of the left ventricle.[5]

### PATHOLOGY

#### CONGENITAL ANOMALIES OF THE MITRAL VALVE

Congenital stenosis and insufficiency of the mitral valve are presented together, as their pathology and associated lesions are similar. Moreover, they frequently coexist in the same patient.

***Supravalvar Mitral Ring.*** A common cause of congenital mitral valve stenosis, the supravalvar mitral ring is an acquired fibrous structure attached to the posterior annulus of the mitral valve, running from both commissures to the mid-height of the anterior leaflet. The lesion is stenotic and often more significant than the extent of the ring would suggest. This is mostly due to the consequent limitation in the opening mechanism of the anterior leaflet rather than to the actual diaphragm-like effect of the ring. Strictly attached to the mitral valve annulus, it is to be differentiated from cor triatriatum (Chapter 80). The supravalvar mitral ring is thought to develop as a consequence of turbulent flow through the mitral orifice. The primary lesion of the mitral

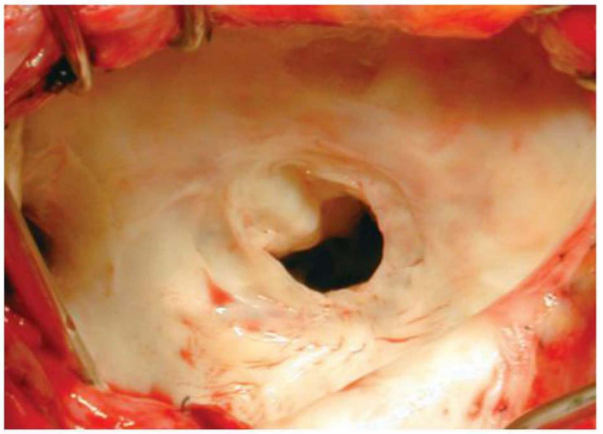


FIGURE 81-1 Supravalvar ring. Intraoperative photograph. Note the implantation of the supravalvar ring high, close to the annulus on the posterior leaflet side (inferior side of the picture) and at the midlevel of the anterior leaflet (left side of the picture).

valve responsible for this turbulent flow can be stenotic or regurgitant or can be very discrete and difficult to identify (Fig. 81-1). It can be related to a prominent coronary sinus, as found in hearts with persistence of the left superior vena cava.[6] The stenosis may be initially functional and created by a very large left-to-right shunt. For these reasons, the supravalvar mitral ring is probably prone to recur after surgical resection unless (or even when) the underlying anatomic anomaly has been identified and corrected. The supravalvar ring can be encountered very early in life, in the neonate or young infant. It should be suspected when a transvalvar gradient appears to increase at follow-up or when the Doppler gradient is greater than what the anatomy depicted with echocardiography would suggest; sometimes, it is only found at operation.

***Cleft Mitral Valve.*** Very often isolated, a cleft mitral valve can be easily differentiated from a left atrioventricular valve in a partial atrioventricular septal defect.[7,8] It is an actual cleft with no suspension apparatus on the edges of the defect. The cleft is centered on the aortic commissure between the noncoronary and left coronary cusps. Each half of the anterior leaflet at midportion bears the attachment of the strut chordae. Both papillary muscles are normal. Rarely, a cleft mitral valve is associated with a leaflet tissue shortening and thickening of the cleft edges. These are acquired lesions secondary to chronic regurgitation through the cleft. The defect is never stenotic and may generate only little regurgitation for a long time.

***Accessory Valve Tissue and Valvular Tags.*** In this specific anomaly, the interchordal spaces are filled with a dense network of immature valve tissue. When there is continuity between the anterior and posterior leaflets, the accessory valvar tissue may be generating a gradient inversely correlated with the size of the perforations in the accessory tissue

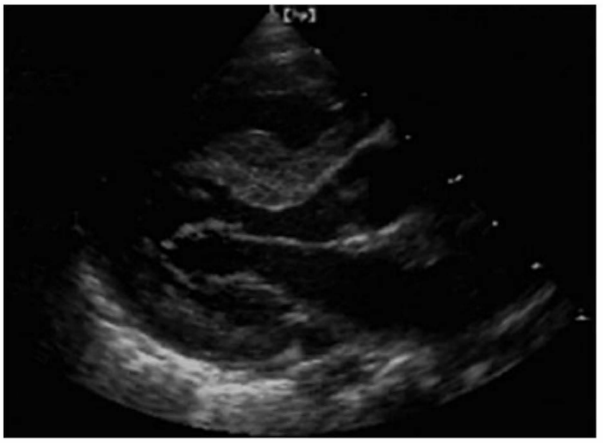


FIGURE 81-2 Accessory mitral valve tissue in diastole.

(Fig. 81-2). When the accessory valve tissue is entrapped in the left ventricular outflow tract, the mitral valve may become regurgitant due to the traction exerted by the accessory valvar tissue on the anterior leaflet, making the valve incompetent in midsystole.[9] Left ventricular outflow tract obstruction is nevertheless the predominant hemodynamic lesion observed with this pathology.[10] Very often, patients are asymptomatic and show no hemodynamic disturbances on echocardiographic studies.

***Lesions Associated with Lack of Valvar Tissue.*** Three major anatomic types of lesions are associated with lack of valvar tissue. The functional endpoint of the lesion can be either normal, predominantly regurgitant or stenotic, or both.

**Parachute Mitral Valve.** A parachute mitral valve (PMV) can be found in isolation and is also observed in association with Shone complex.[11,12] The most common finding is that of a predominant single papillary muscle with the orifice of the mitral valve overriding its tip. With this particular pathology, there is a spectrum of abnormality of the suspension apparatus, ranging from complete fusion of the tip of the papillary muscle to the free edge of the valve to relatively normal-looking chordae with good mobility of the leaflet. Accessory papillary muscles are usually very small and connected to only a short segment of the free edge or even to the undersurface of the leaflet tissue (as would be the case in a larger-than-normal secondary chorda). The functional anatomy of the PMV depends on the interaction between the amount of tissue and the mobility of the leaflet, the presence and size of the fenestrations, and the presence, length, and quality of the chordae.[11] The PMV almost always has a stenotic component. Double-orifice mitral valve is an exceedingly rare variant of PMV, with the lesser papillary muscle supporting a complete orifice. This lesion should be differentiated from the left atrioventricular valve, in which an accessory orifice is often found in the case of diminutive or absent left lateral leaflet (mural leaflet). The second orifice is almost always competent and should not be closed at the time of the repair.



FIGURE 81-3 Papillary muscle to commissure fusion. Postmortem photograph.

**Papillary Muscle-Commissure Fusion.**[11] This anomaly, which can be limited to only one papillary muscle, ranges from cases with short chordae to those in which the tip of the papillary muscle is actually directly attached or fused to the commissural area of the free edge. The valve is generally more regurgitant than restrictive; this is due to the lack of valvar tissue and the consequent restriction of leaflet motion (Fig. 81-3). When the papillary muscles are hypertrophied, the bulk of their mass is generally responsible for a predominantly restrictive physiology. Some Anglo-Saxon authors refer to this anatomy as arcade mitral valve.[4]

**Hammock Valve (Arcade Mitral Valve).**[11] Here the suspension apparatus may have lost all resemblance to the normal anatomy. No papillary muscle may be identifiable or there may be multiple very small ones behind the posterior leaflet. The leaflets are suspended by a network of chordae directly attached to the posterior wall of the ventricle. This attachment is generally displaced toward the base of the heart, with an excess of tension on the anterior leaflet and extreme limitation in the motion of the posterior leaflet. The valve is most often predominantly regurgitant.

***Regurgitant Mitral Valves with Normal Anatomy Associated with Congenital Cardiac Lesions.*** It is difficult to ascertain the congenital origin of these lesions, since the anatomy of the mitral valve is otherwise normal. Although most publications on congenital anomalies of the mitral valve include them,[12] there is no evidence of their congenital origin. Unlike the previously mentioned anomalies, they are in fact not found at birth. They are usually associated with conditions characterized by significant volume loading of the left ventricle [i.e., large ventricular septal defect (VSD) or large patent ductus arteriosus]. The pathophysiology is that of initial dilation of the posterior annulus due to the effect of the increase in volume overload. Secondarily, the marginal chordae elongate and create prolapse of the free edge of the anterior leaflet. These lesions are not rare, as they account for 15 to 40 percent of the patients reported in the literature with congenital mitral valve regurgitation. Functional mitral regurgitation secondary to cardiomyopathy is not included in this chapter.

**Anomalous Left Coronary Artery from the Left Pulmonary Artery.** Mitral valve regurgitation found in an anomalous left coronary artery from the left pulmonary artery (ALCAPA) is of ischemic origin and is described in detail in Chapter 83. In this particular anomaly, mitral regurgitation is a constant finding and is quantitatively almost always greater than moderate. The typical patient is between 2 and 4 months of age at diagnosis. Correction of the ALCAPA reduces the grade of regurgitation but rarely suppresses it entirely. Structural modification of the suspension apparatus with infarction of the anterolateral papillary muscle and elongation of the chordae originating from the latter usually prevent complete regression of the regurgitation without concomitant mitral valve repair at some point.[13]

***Mitral Valve Disease with Excess Leaflet Tissue: Mitral Valve Prolapse and Connective Tissue Disorder.*** Whether to include the mitral valve prolapse syndrome (limited in its more common form to the middle scallop of the posterior leaflet) in the congenital group is debatable. The histologic anomalies are limited in adults to the middle scallop of the posterior leaflet, with predominant alteration of the elastic fibers and proliferation of myxomatous tissue; these anomalies, in all likelihood, have a genetic etiology.[14,15] In the more extensive form of mitral valve prolapse (Barlow's disease, with excess of tissue distributed to both the anterior and posterior leaflets), histology demonstrates extensive infiltration of the spongiosa with myxomatous tissue. This more extensive form can also be seen in neonates and infants. It is encountered in sporadic cases or in familial forms and has been associated with at least one locus mutation on chromosome 16. The histologic anomalies are identical to those found in Marfan,[16] Loeys–Dietz, and Elher–Danlos syndromes. Similar valvar alterations are found in Hurler syndrome (mucopolysaccharidosis type I).

## ACQUIRED MITRAL VALVE DISEASE

***Rheumatic Heart Disease.*** Acute rheumatic fever (ARF) is an autoimmune disorder in which the immune response to group A streptococcal (GAS) M protein generates T cells and antibodies that cross-react with cardiac antigens.[17,18] ARF does not generate long-term sequelae to brain, joints, or skin. Only the heart (specifically the mitral and/or aortic valves) may be permanently affected. The acute damage to the valves may cause chronic and evolving lesions secondary to the scarring process and/or to modifications in hemodynamics. This chronic picture is known as rheumatic heart disease

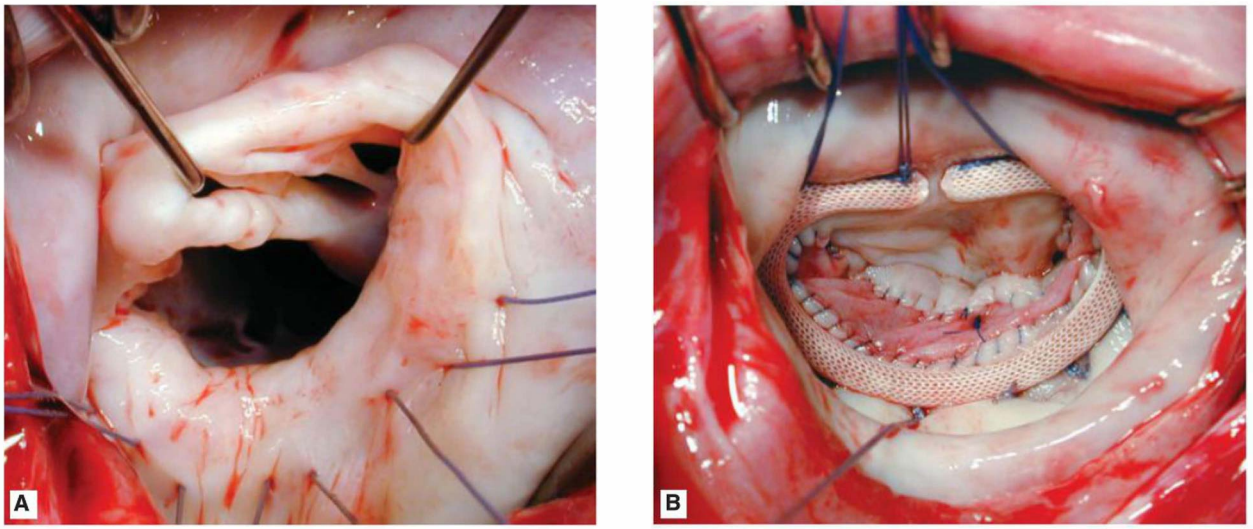



**FIGURE 81-4** **A.** Chronic evolved rheumatic mitral insufficiency. The anterior and posterior leaflets are severely retracted. There is limitation of the posterior leaflet motion, prolapse of the anterior leaflet, commissural fusion, and paucity of chordae, which are thickened and fused. **B.** Repair with posterior leaflet extension, correction of anterior type II and remodeling annuloplasty.

(RHD), which is the most common pediatric heart disease in developing countries. Not all individuals are equally susceptible to ARF. Only 3 to 5 percent have an inherited susceptibility, although the basis of this is unknown. Also, only a limited number of GAS strains can initiate ARF in the susceptible host.

**Acute Lesions.** Acute lesions are exclusively regurgitant. On inspection, the valvar tissue and chordae are swollen but supple. Prolapse of either leaflet can be seen, but the anterior leaflet is predominantly affected.[19] This prolapse is usually related to elongation of limited groups of chordae, while chordal rupture is rare. Multiple small nodules (2–3 mm in diameter) can be seen on the free edge of either of the mitral leaflets. Mitral regurgitation is a combination of annular dilation (secondary to rheumatic pancarditis) and various degrees of prolapse.

**Chronic Lesions.** The scarring process generates retraction of the valvar tissue and, to a lesser degree, the chordae. This process is sometimes sufficient to correct the prolapse of the acute phase. The healing of the spongiosa induces fusion of chordae, as demonstrated by the dramatic reduction in the number of chordae together with the large increase in their size. The physiology of the regurgitation is a combination of prolapse of the anterior leaflet, retraction of the posterior leaflet, and annular dilation (Fig. 81-4). In the pediatric age group, the mitral valve is exclusively or predominantly regurgitant, while stenosis typically appears later in the chronic phase of the disease with continuation of the retraction process. The degree of stenosis and the age at which stenoses can be found varies from population to population. The younger the age during the primary attack of rheumatic fever, the younger the patient when stenosis appears. Other factors may play a role. Calcifications are rare in the pediatric population with RHD.

***Infective Endocarditis.*** Bacterial endocarditis (BE) of the mitral valve is rare and, excluding patients with RHD, represents less than 2 percent of all BE in children. At the Royal Children's Hospital (RCH), Melbourne, a history of mitral valve anomaly before the diagnosis of BE was uncommon. The resulting physiology is always that of a regurgitant lesion. Intraoperatively, a vegetation is the most common finding and typically grows on the atrial side of the mitral valve; however, vegetations are not always present at the time of surgery. Rarely the vegetation will have embolized and, more commonly, it will either regress with medical therapy or have never been there. Other findings are perforation of the leaflet (Fig. 81-5), abscess formation within the mitral annulus, or extension toward the aortic valve. Histologic examination of vegetations discloses microorganism-infiltrated fibrin thrombi. Findings in the affected valvar tissue at the vegetation implantation site suggest a strong inflammatory reaction with neovascularization and infiltration of lymphocytes, giant cells, and fibroblasts. At the time of surgical repair, it is very important to differentiate intact valvar tissue (supple, thin, and resistant) from infected tissue (thickened, edematous, and friable).

## CLINICAL FEATURES AND PRESENTATION

### NEONATES AND YOUNG INFANTS

For both stenosis and regurgitation, the clinical presentation in this age group includes cardiac failure, with dyspnea on exertion (feeding) and tachypnea at rest. Severe failure to thrive

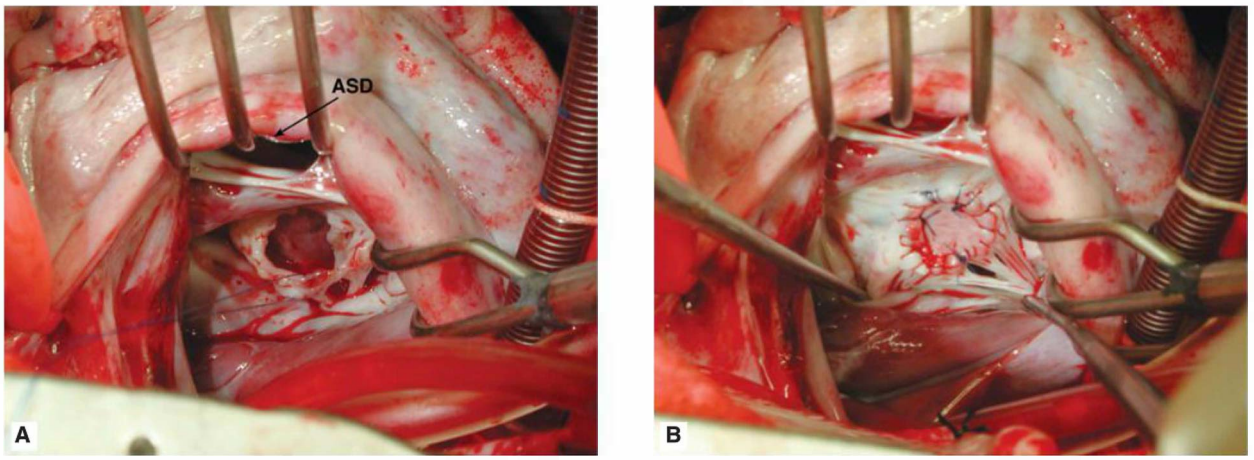



**FIGURE 81-5** Acute endocarditis of the mitral valve. Perforation of the anterior leaflet (**A**). Result following the repair with autologous pericardium treated with glutaraldehyde (**B**). ASD, atrial septal defect. (Image courtesy of Luca Vricella, Division of Cardiac Surgery, The Johns Hopkins University.)

is usually present. Clinical examination shows hepatomegaly and cool extremities. Cyanosis may be present. Auscultation is often unyelding, but a strong apical systolic murmur should indicate significant mitral regurgitation, whereas a diastolic murmur in the case of mitral stenosis can be difficult to auscultate or may even be absent in the context of low cardiac output or associated atrial-level left-to-right shunting.

### OLDER INFANTS AND TODDLERS

Beyond the neonatal period, failure to thrive, dyspnea on exertion, and a history of repeated chest infections are predominant in mitral stenosis. Pallor and cold extremities, tachycardia, and dyspnea suggest low cardiac output. Signs of pulmonary hypertension, with an exacerbated second heart sound, prominent right ventricular impulse, and hepatomegaly are frequent. A diminished first sound with a low-intensity mid-diastolic murmur suggests thickened leaflets with limited excursion and can be absent in a low-output state. Older infants and toddlers with mitral regurgitation present with various degrees of failure to thrive and dyspnea with feeds or on exertion. An enlarged left ventricular impulse (with a high-frequency, high-intensity holosystolic murmur heard at the apex and extending into the axillae) is easily auscultated, with signs of right heart failure rarely being seen.

## Diagnostic Modalities in Mitral Valve Disease

### ELECTROCARDIOGRAPHY

There is left atrial enlargement in both mitral stenosis and regurgitation and left ventricular enlargement in mitral regurgitation; right atrial and right ventricular enlargement is seen when pulmonary hypertension is present. In the pediatric population, the rhythm is almost always sinus.

### CHEST X-RAY

Chest x-ray will typically demonstrate the "double density" seen in left atrial enlargement; this is more often the case in regurgitation than in stenosis; other findings are those of variable pulmonary plethora and enlarged contour of the main pulmonary artery. In the presence of mitral valve regurgitation, left ventricular enlargement is responsible for most of the prominence of the cardiac silhouette.

### ECHOCARDIOGRAPHY

Echocardiographic assessment is obligatory and essential. Systematically conducted, it provides all the information necessary to diagnose the mitral anomaly, determine its severity,[20,29] and assist the surgeon with the repair.[21,30]

The transthoracic four-chamber view is best for obtaining an accurate transvalvar gradient and, together with the parasternal long axis view, defining the precise amplitude of any prolapse or restriction; in general, it is much more accurate than other views in grading the degree of regurgitation. The short-axis view of the mitral valve and the left ventricle provides direct imaging of the area of the mitral orifice as well as the location of origin of the regurgitation jet (in the *en face* view). It allows a precise analysis of the papillary muscles (presence, size, location, and symmetry) and of anterior leaflet integrity. Transesophageal echocardiography (TEE) is superior in defining the anatomic details of the suspension apparatus and evaluating the functional classification. By moving the probe within the esophagus, the operator can obtain precise localization of the area of prolapse along the free edge of the anterior leaflet, using the anterior commissure (probe up) and the posterior commissure (probe down) as anatomic landmarks.

For mitral stenosis, the peak instantaneous and mean gradients across the valve must be interpreted according to the quality of diastolic function and of associated lesions. The overall impact of the gradient on the surgical indication

must be weighed against pulmonary artery pressure and clinical context.

***Functional Classification.*** Transthoracic echocardiography (TTE) and TEE make it possible to classify mitral valve pathology, according to the motion of the leaflets, into one of the three following types (Carpentier's functional classification). This classification is irrespective of anatomy and etiology but is essential for carrying out accurately the repair.[22,31]

**Type I: Normal Leaflet Motion.** Mitral regurgitation results from a lack of coaptation between the leaflets.

**Type II: Leaflet Prolapse.** The free edge of one or both leaflets overrides the plane of the orifice during systole.

**Type III: Restricted Leaflet Motion.** The motion of one or both leaflets is limited. This can be secondary to short or stiff leaflet tissue or suspension apparatus (type IIIa or diastolic) or because the leaflet is pulled away from the coaptation area by a paradoxical motion of the ventricular wall (type IIIb or systolic).

### THREE-DIMENSIONAL ECHOCARDIOGRAPHY

Currently, the major benefit of three-dimensional (3-D) echocardiography is to provide a surgical view of the mitral valve to the surgeon (from the atrium, with the anterior commissure to the left and the posterior commissure to the right) and to precisely localize on this view the prolapse and restriction of the leaflets. 3-D echocardiography has made very important progress in the past few years. Pediatric probes are now available and can be inserted in patients smaller than 5 kg. Even if spatial definition, speed of acquisition and slice thickness have improved, thin and fast-moving structures like leaflet tissue and chordae are less well seen in infants and young children than in adults. In larger patients (weighing more than 12 kg), information on the origin of the regurgitant jet, the volume of the jet, and ventricular ejection volume can be obtained as in adults.[23]

### MAGNETIC RESONANCE IMAGING AND ELECTRON-BEAM COMPUTED TOMOGRAPHY

Computed tomography (CT) allows precise calculation of the mitral valve regurgitant fraction with flow measurement, so does magnetic resonance imaging (MRI) when correction for the modification of the plane of the valve with three-directional velocity-encoded MRI is used. The mitral valve area is calculated with MRI, and correlations with echocardiographic findings are very strong.[24] Whatever the imaging technique employed, there are limitations in small patients, in whom resolution is critical. Neither MRI nor CT has enough spatial resolution to visualize valvar tissue or suspension apparatus in small children.

### DIAGNOSTIC CARDIAC CATHETERIZATION

In the current era, there is very limited indication for an invasive diagnostic and hemodynamic study in the assessment of mitral valve disease. Associated lesion or consideration for balloon valvuloplasty may warrant cardiac catheterization.

### LABORATORY DIAGNOSTIC MODALITIES IN RHEUMATIC FEVER

There is no laboratory test for the diagnosis of ARF, hence the diagnosis remains clinical. The diagnosis requires the evidence of a preceding GAS infection (elevated or rising antistreptolysin O titers, a positive throat culture, or positive rapid antigen test for group A streptococci); although this is necessary, it is not sufficient. The probability of a diagnosis of ARF varies according to geographic location (according to ARF incidence) and ethnicity. For diagnostic purposes, clinicians follow Jones's criteria, updated in 1992.[25]

## Treatment

### MEDICAL THERAPY

Medical treatment must be vigorous when the annulus is too small to allow implantation of a mechanical prosthesis in the anatomic position. In the setting of predominant mitral regurgitation, the treatment should include diuretics, and, if necessary, blood transfusion[26] and positive pressure ventilatory support. In patients who do not yet require surgery, the benefit of angiotensin-converting enzyme (ACE) inhibitors is not clear.[27] In mitral stenosis, any vasodilator or afterload-reducing agent is obviously contraindicated.

### SURGICAL TREATMENT

***Indications.*** Indications for surgical intervention in chidren are different than in adults. Within the pediatric age group, the cut-off point is more related to the size of the mitral valve annulus than to the age of the patient. The rationale for this is in the risk involved with valve replacement in nonanatomical position or with oversized prosthesis.

**Large Mitral Valve Annulus.** "Large" implies an annulus greater than 30 mm in female patients and greater than 32 mm in males. Using a wide range of mitral valve repair techniques, the probability of a successful repair of the valve with a large annulus is very high. A mitral annuloplasty or even a remodeling annuloplasty will not be outgrown and will not generate stenosis with the growth of the patient. The repair of virtually all valves is, when a sizeable annulus is present, an accessible goal.

**Small Mitral Valve Annulus.** In neonates (<28 days), infants (>28 days and <1 year), and generally in every pediatric patient with a mitral valve annulus less than 19-20 mm in size, repair is technically very challenging, while replacement is possible only with the use of surgical artifacts

associated with significantly increased mortality.[28] In these patients, surgical intervention should be deferred as long as the patient can be managed with intense medical therapy, including transfusion and continuous positive airway pressure (CPAP). Aggressive medical therapy allows, in some cases, postponement of surgical intervention for several months, often generating significantly more favorable operating conditions.

**Intermediate Mitral Valve Annulus.** In these patients, with a mitral valve annulus greater than 20 mm but smaller than adult size, mitral valve replacement (MVR) can be safely performed in the anatomic position.[29] Therefore, the timing of the mitral valve repair does not have to be delayed for fear of replacement in an unfavorable position. In this age group, this anatomic situation is found in patients between the ages of 1 to 12 years; it is generally safe to wait for quite a long time (up to several years) in cases of severe regurgitation provided that adequate monitoring of pulmonary artery pressure and ventricular function is achieved.[30,31]

***Mitral Valve Repair.*** At our institution, cardiopulmonary bypass is conducted with moderate hypothermia (32°C), hemoglobin of 10 to 12 g/dL, pump flow of 150 to 200 mL/min/kg, or 2.4 L/min/$m^2$. Myocardial protection is achieved with warm blood cardioplegia administered every 20 min. The time for preparation for bypass is used for mandatory intraoperative TEE. Venous cannulation should allow as much access as possible to the atrioventricular groove. Direct cannulation of the superior vena cava at a distance from the cavoatrial junction and of the inferior vena cava immediately at its origin allows for precise application of the retractor blades. Limited dissection of the groove is performed and, after cross-clamping, the left atrium is entered in the interatrial groove. Exposure is enhanced with mattress sutures inserted into the posterior annulus, pulling the valve upward and to the right, toward the operator. The tourniquet on the inferior vena cava is pulled upward and to the left. A self-retaining retractor for mitral surgery adapted to the size of the patient is used in our practice. Approach through the interatrial septum provides a lesser edge for anchoring of the retractor blades and exposes the conduction tissue to more pressure. Approach through the roof of the left atrium does not expose the posterior commissure and the posterior papillary muscle well. We also believe that the ranseptal approach provides lesser exposure.

Once satisfactory exposure of the mitral valve is achieved, the valve is systematically analyzed and findings are compared with the echocardiographic information. The functional classification is confirmed as well as its location (A1, A2 or A3, P1, P2 or P3), but the extent of the mitral valve prolapse or restriction is based on echocardiographic studies of the beating heart. Then analysis of the anatomy follows: a supravalvar ring is confirmed or eliminated; the diameter of the annulus is carefully assessed; texture, aspect, and size of the mitral valve leaflets are noted; the presence and location of any jet lesion is determined as well as the number, aspect, and distribution of the chordae; finally, the presence of commissural tissue and dedicated suspension apparatus as well as the size, location, and morphology of the papillary muscles are assessed. The examination ends with a careful check for accessory mitral valve tissue in the interchordal spaces. The diameter of the annulus and of the opening of the mitral valve is compared to the normal values reported for the patient's body surface area. We use a modification of the sizes provided by Kirklin.[32] The treatment is adapted to the predominant functional class.

**Correction of Type I Functional Abnormalities.** With the exception of some isolated type I abnormalities without annular dilation (mostly the cleft mitral valve), an annuloplasty is mandatory in all cases of mitral valve insufficiency. In most other cases, attempts to perform mitral valve repair without annuloplasty have resulted in recurrence.[12] In order to accommodate an adult-size device or a larger-size annulus than what would be indicated from the area of the anterior leaflet, leaflet enlargement with glutaraldehyde-treated autologous pericardium of the posterior leaflet (Fig. 81-6), the anterior leaflet (Fig. 81-7), or both are used.[12,33] When no remodeling annuloplasty is available for the size of the patient or the device is thought to be too small, an annuloplasty limited to the posterior annulus is indicated. The annuloplasty must incorporate both fibrous trigones and can be interrupted to allow for further growth. In our hands, the best method for posterior annuloplasty, allowing for growth without compromising the inflow, is a row of interrupted

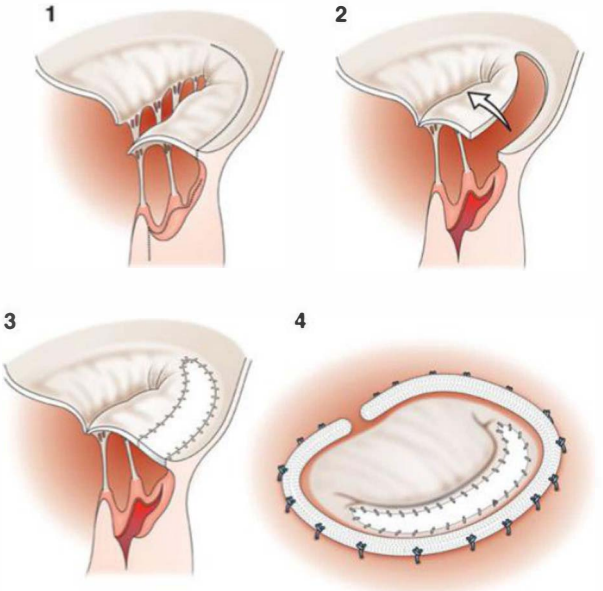



**FIGURE 81-6** Detachment of the posterior leaflet allows access to the suspension apparatus for mobilization (here in a hammock valve). The patch enlargement of the posterior leaflet treats the type III and allows for a larger annuloplasty.

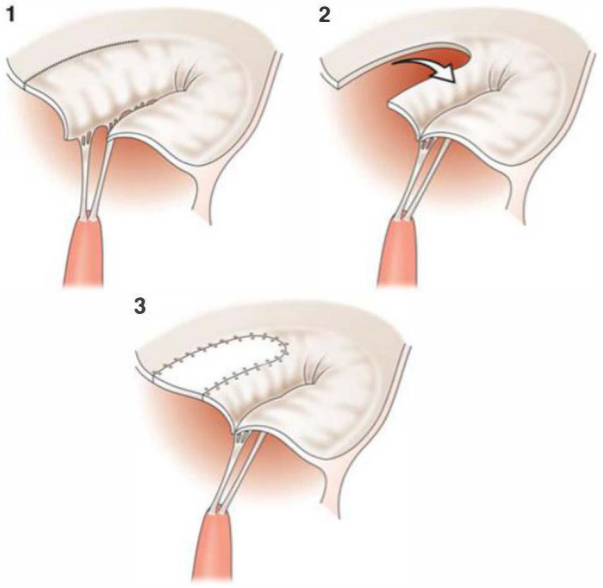



FIGURE 81-7 Patch enlargement of the anterior leaflet to treat the lack of tissue in congenital valve or the retraction of the rheumatic leaflet.

compression U stitches tied individually (Fig. 81-8).[21] Also, for bigger patients, a single layer of ePTFE (expanded polytetrafluoroethylene/Goretex) band can be used. We try to avoid bulky material in small annuli; this can be later responsible for fibrosis of the posterior leaflet.[34]

**Correction of Type II Functional Abnormalities.** Multiple techniques are available to correct the enhanced leaflet motion seen in this functional class. Whether these techniques are to be used in isolation or in combination depends on the extension in width of the prolapse (localized or extended to the whole width of the free edge). It is the height of the prolapse (based on the findings of TEE) and the quality of the chordae that will dictate the choice of technique.

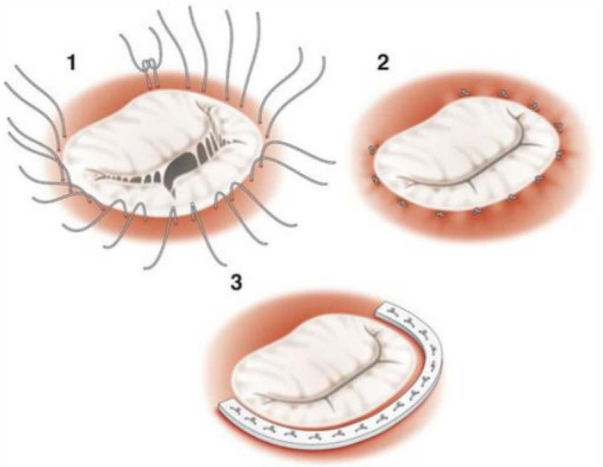



FIGURE 81-8 Annuloplasty limited to the posterior annulus in patients with less than adult size annulus. Two techniques are represented and used at the Royal Children's Hospital, Melbourne. Mattress sutures are implanted along the posterior annulus from one commissure to the other. (1) The mattress sutures are tied over themselves and compress the annulus. (2) A band of PTFE is used to calibrate the shortening. Care is taken not to overtighten the knots.

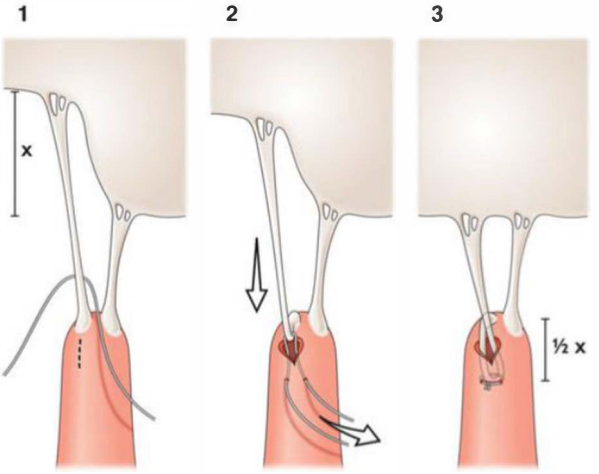



FIGURE 81-9 Chordal shortening: Note the extent of the shortening achieved.

As long as the anatomic correction is adequate (restoring a large surface of apposition between the anterior and posterior leaflets), all techniques are effective and reliable. Overcorrection will generate stress directly on the repaired area and deprive the valve of the relief of stress provided by the surface of apposition. All overcorrections eventually fail, most often in the first few days postoperatively.

*Chordal shortening.* This technique requires thin and flexible chordae.[22] This form of correction generates important shortening of the chordae and is only adopted when the prolapse is wide (Fig. 81-9). It is a time-consuming procedure and is to be considered if multiple chordae are to be shortened, requiring also access to the mid-height level of the papillary muscles.

*Chordal transfer.* Chordal transfer between secondary chordae and the free edge (more than chordal transfer from the posterior leaflet to the anterior leaflet) allows for correction of localized prolapse. The chorda should be detached from the body of the anterior leaflet with a minimal amount of valvar tissue. It is then attached to the free edge directly at the required length with a small running suture (Fig. 81-10).

*Wedge resection of the papillary muscle.* Wedge resection of the papillary muscle (Fig. 81-11) and sliding plasty (Fig. 81-12) generate different degrees of correction of prolapse of multiple chordae. These techniques are very well adapted to prolapse involving a large segment of the anterior leaflet.

*Papillary muscle shortening.* This technique can be used in combined anterior and posterior type II deformity. It is useful

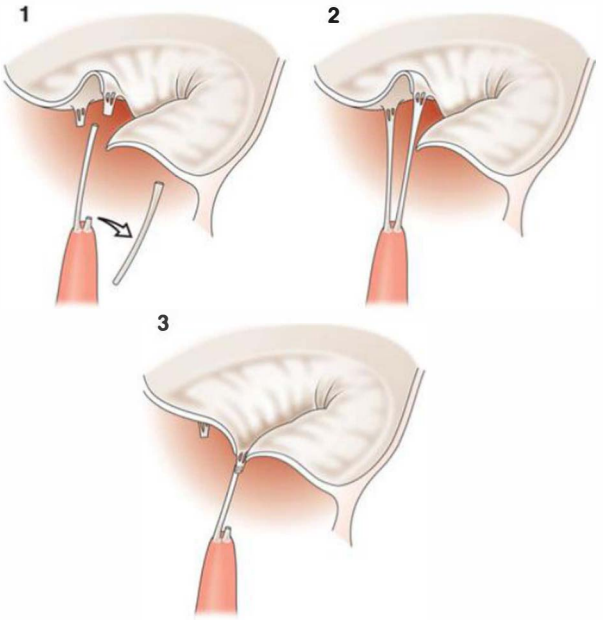



FIGURE 81-10 Chordal transfer: Only secondary chordae should be used and *not* the basal chordae.

when the papillary muscle as a whole has to be shortened, as is usually the case in chronic ischemic papillary muscle or in Barlow's disease (Fig. 81-13).

*Artificial chordae.* Artificial chordae should be used only in the absence of available chordae of appropriate strength and quality in the area of prolapse. The insertion requires rigorous technique to avoid overcorrection and large knots at the free edge (Fig. 81-14).

**Correction of Type III Functional Abnormalities.** Successful correction of restricted leaflet motion and insufficient

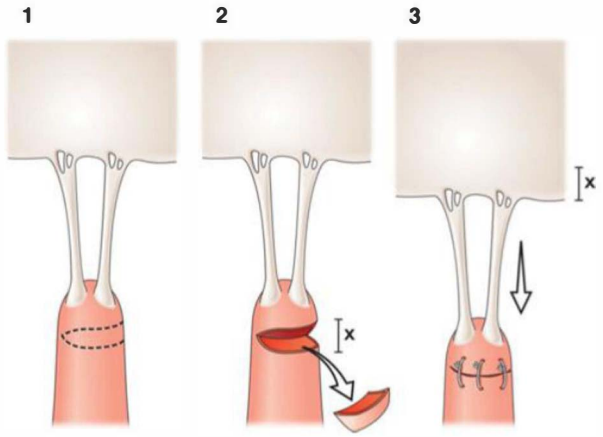



FIGURE 81-11 Wedge resection: Achieves limited shortening distributed to several chordae.

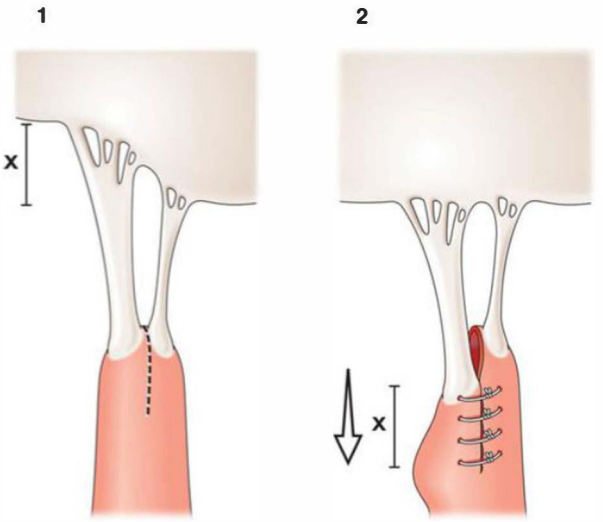



FIGURE 81-12 Sliding plasty: achieves controlled shortening for thickened chordae.

leaflet tissue is the essence of working with congenital mitral anomalies, especially in the first year of life. It falls into three general categories:

1. *Posterior leaflet mobilization and enlargement associated with mobilization of the papillary muscles.* Access to the suspension apparatus is the key to adequate mobilization of the latter. It can be done through the mitral valve orifice when it is sufficiently large. Most often, it is very small and does not allow for good access to the suspension apparatus. In these situations, detachment of the posterior leaflet generates a good view of the papillary muscles. Adequate thinning, mobilization from the posterior wall, and splitting and fenestration of the papillary muscles can then be performed safely with good exposure. After full mobilization, the posterior leaflet is reconstructed with enlargement of the valvar tissue (see Fig. 81-6).[12,21]
2. *Enlargement of valvar tissue using autologous pericardium treated with glutaraldehyde.* Augmentation of the valvar

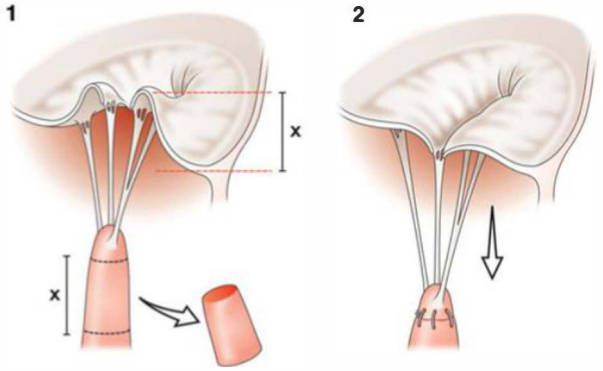



FIGURE 81-13 Papillary muscle shortening by resection and reconstruction.

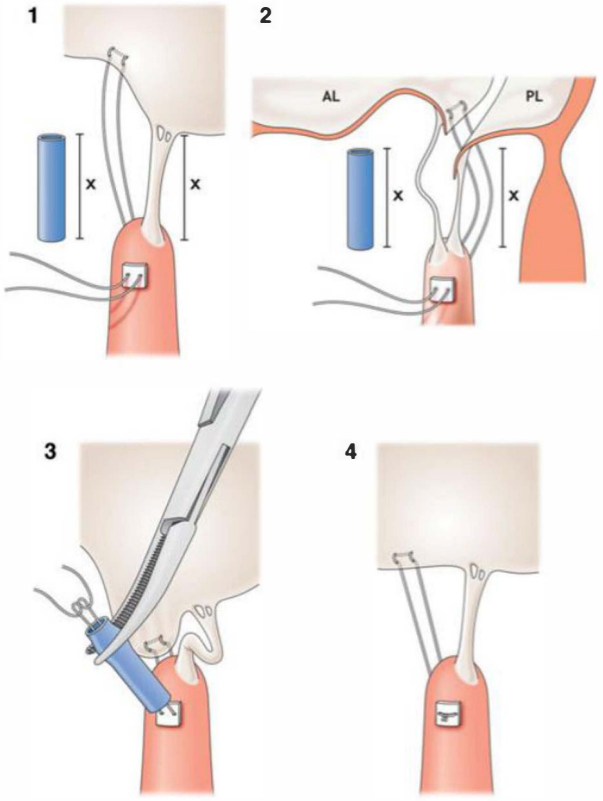



**FIGURE 81-14** Technique for insertion of ePTFE chordae: (1) A template is made from a short plastic tube cut at the required length and slid over the distal part of the stitch. (2) This template can be taken from the facing posterior leaflet edge. (3) The free edge of the leaflet is lowered to the contact of the papillary muscle. The artificial chordae is tied while the template is clamped. (4) The template is removed and the mattress suture is pulled to bring the knot in contact of the papillary muscle.

leaflet tissue is the only way to treat a lack of valvar tissue. It can be limited to the anterior leaflet (see Figs. 81-6 and 81-7) or the posterior leaflet or be used for both. Extension of the posterior leaflet should be limited to less than half of the height of the leaflet. It can be limited to the area of the middle scallop; alternatively, when the detachment extends from one commissure to another, the extension should reproduce a shape with three scallops and two subcommissures to allow for a large opening in diastole. Extension of the anterior leaflet should be done in the body of the leaflet (leaving a strip of valvar tissue close to the hinge point) in order to avoid mechanical stress at this level. The height of the extension should not be greater than two-fifths of the height of the anterior leaflet, leaving the area close to the free edge intact to allow for a supple and efficient surface of coaptation. Unless required by a specific anatomy, the enlargement should be symmetrical from trigone to trigone.

3. *Resection of supravalvar rings and accessory mitral valve tissue.* Resection of supravalvar tissue requires excellent exposure of the leaflets. The supravalvar tissue can sometimes be peeled off the valvar tissue. More often, there will be the need for a careful cleavage plane with blunt dissection. Perforation of the anterior leaflet may occur; this should be closed with a figure-of-eight suture (Fig. 81-15). The resection of accessory mitral valve tissue requires a similarly rigorous surgical technique, and very good exposure of the subvalvar apparatus is needed to perfectly differentiate the mitral valve chordae from what can be resected without compromising the integrity of the suspension apparatus. Various approaches to the suspension apparatus may have to be combined: through the mitral valve orifice and the aortic valve or by detachment of the posterior leaflet (Fig. 81-16).

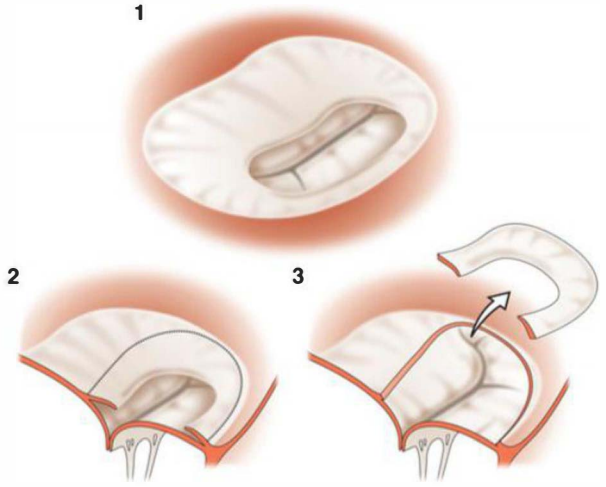



**FIGURE 81-15** Excision of supravalvar mitral ring.

***Valve Replacement.*** MVR should be avoided at all costs in pediatric patients; however, it may be the only option when the valve cannot be repaired. The risk of death in pediatric MVR with a mechanical prosthesis increases with the

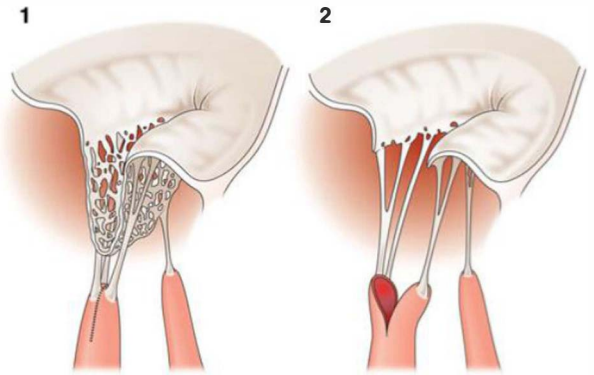



**FIGURE 81-16** Excision of extra valvular tissue, here within a parachute mitral valve. Great care must be taken to preserve the suspension apparatus.

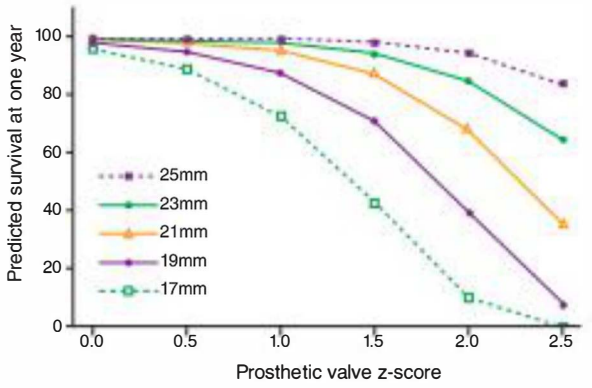



**FIGURE 81-17** Predicted survival at 1 year is plotted against prosthetic valve *z*-score. Note that as disparity between prosthetic valve size and normal mitral annulus size increases (increasing *z*-score), 1-year survival falls precipitously. This effect is greatest at smaller valve sizes. (Reproduced with permission from Caldarone CA, Raghuveer G, Hills CB, et al. Long-term survival after mitral valve replacement in children aged <5 years: A multi-institutional study. *Circulation* 2001;104 (12 Suppl 1):I143–I147.)

prosthetic size/body-weight ratio, with highest mortality in patients with smaller annular diameters (Fig. 81-17).[35]

**Mitral Valve Replacement in the Supra-annular Position in Infants.** This procedure should be avoided as much as possible because it is responsible for the majority (or totality) of perioperative and late deaths in units with experience with MVR in children.[28] Mitral valve repair is often a palliation or a short-term palliation, but allows for annular growth and eventually replacement with a larger prosthesis.

**Mitral Valve Replacement with a Larger Annulus.** This is now possible with excellent long-term results, and only mechanical valves should be implanted in pediatric patients. The introduction of low-profile aortic valves has proven to be very useful in the management of pediatric MVR, since in patients with smaller annular diameters (=20 mm), an aortic prosthesis can be implanted in an "upside-down" position. Bioprostheses have been associated with early degeneration and the need for reoperation in younger patients,[36] and mitral valve homografts have not produced satisfactory results in children.[37]

***Replacement of Mechanical Prostheses.*** This procedure has become not uncommon in most pediatric units. The need for prosthesis replacement is dictated by the size of the first prosthesis implanted and the age at first implantation.[38] The indication is usually the development of a transmitral gradient with pulmonary hypertension, at rest or during exertion. A larger size prosthesis can usually be implanted, but it is in rare instances more than two sizes larger than the one previously implanted. For a 17-mm mechanical prosthesis implanted in infancy, two further valve replacements will typically be required until a 25-mm mechanical valve can be implanted. On the other hand, a palliative repair should allow for a larger prosthesis to be implanted at the time of the first MVR. Technically, the replacement of a pediatric mechanical prosthesis differs significantly from the same procedure in the adult. Great care must be taken to remove all cuff tissue and pledgets; everting mattress sutures (especially with pledgets) should be avoided, as they may reduce the size of the annulus. Preference is given in our practice to simple interrupted sutures.

### *Special Considerations*

**Rheumatic Heart Disease in Children.** Appropriate timing for mitral valve repair in children with RHD is essential but unfortunately rarely achieved. Surgery should be delayed from the acute rheumatic episode to allow for spontaneous regression of regurgitation with attenuation of the carditis under appropriate treatment. Early surgery is more difficult, as tissues are swollen and fragile. Mitral valve repair during the acute phase of RHD carries high recurrence rates.

At the RCH, Melbourne, we favor a short period of follow-up (6-12 months) when severe mitral regurgitation has become chronic. At that time, morphologic conditions are usually better than those encountered earlier than 12 months after the acute phase. The leaflets should still be thin and pliable, and the suspension apparatus moderately elongated but not thickened. Under such operating conditions, excellent results can be achieved with a low residual inflow gradient.

Operation on long-standing chronic mitral valve regurgitation will, on the contrary, generate difficult operating conditions: severe retraction of both leaflets, intense thickening of the suspension apparatus, and commissural fusion with fibrosis and sometimes calcification even in pediatric age group.

**Bacterial Endocarditis.** We advocate very aggressive and early intervention for infective BE in children. When mitral regurgitation is greater than moderate, and as soon as the antibiotic therapy is initiated, we believe that surgery is indicated to prevent further damage of the valve or extension of the endocarditic process to the aortic valve.

## Outcomes

### MITRAL VALVE REPAIR

***Neonates and Infants.*** Between 1996 and 2006 at the RCH in Melbourne, 22 patients less than 1 year of age underwent mitral valve repair. Thirteen with predominant mitral valve regurgitation and nine with predominant mitral valve stenosis. All infants underwent initial valve repair, with three reinterventions in the regurgitation group. There was one early death in a neonate with severe Marfan syndrome, which was unrelated to an otherwise successful mitral valve repair, and one late death.

During the same time interval, nine patients with a median age of 5 months (range 1 week to 10 months) were operated for congenital mitral stenosis. All had severe failure to thrive and severe pulmonary hypertension. The mean

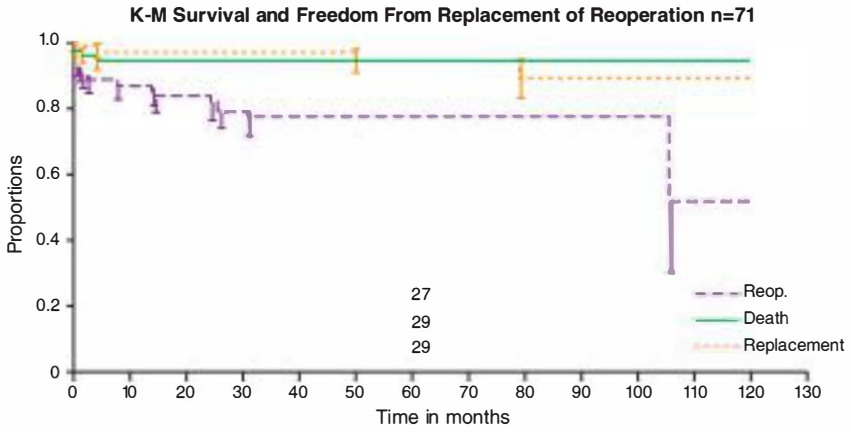



**FIGURE 81-18** Actuarial freedom from reoperation and death or reoperation for repair of congenital mitral valve regurgitation at the Royal Children's Hospital, Melbourne, between 1996 and 2006. (From Oppido G, Davies B, McMullan DM, et al. Surgical treatment of congenital mitral valve disease: Midterm results of a repair-oriented policy. *J Thorac Cardiovasc Surg* 2008;135(6):1313–1320.)

preoperative gradient was 13 ± 2.3 mm Hg. The underlying malformations included papillary muscle-commissure fusion ($n = 6$), PMV ($n = 2$) and supravalvar ring ($n = 1$). Three patients had reoperations. The first patient had three reoperations, leading ultimately to MVR with a mechanical valve. The second patient (neonatal Shone's complex and interrupted aortic arch) underwent reoperation (resection of supravalvar membrane) 2 years following initial intervention. Other teams have similar results in this age group, justifying early operation in severely symptomatic patients.[39]

***Outcomes Beyond Infancy.*** From the most recent available literature,[12,21,40,41] repair should be suitable for more than 90 percent of patients in this age group with mitral regurgitation, with operative mortality below 10 percent and expected reoperation rates lower than 15 percent at 15 years (Fig. 81-18). Hospital mortality should be low when mitral stenosis is isolated. Mitral stenosis with associated cardiac lesions generates higher mortality and reoperation rates, but such associations are rare beyond infancy. After mitral valve repair for mitral stenosis, residual gradients are frequent but are often well tolerated, with the need for reintervention indicated by the level of pulmonary hypertension.

***Rheumatic Mitral Valves.*** In centers with large surgical volumes, successful mitral valve repair can be accomplished in greater than 90 percent of pediatric patients with RHD,[42] with operative mortality often below 2 percent. Large variations in reoperation rates are reported (from <10 to 45 percent at 5 years).[43] This variability could be attributed to the quality of the follow-up, but, most importantly, to compliance with secondary antibiotic prophylaxis and also access to reoperation. In analyzing the success of surgical mitral valve repair, the age of the patient at the time of the first rheumatic episode and the interval to surgical intervention is also to be considered as a potential factor. At our institution, 88 patients (6–24 years of age) have undergone surgery for rheumatic mitral valve insufficiency between 1996 and 2005. All patients underwent initial mitral valve repair. Freedom from reoperation at 70 months (32 patients at risk) was 78 percent. There were 15 reoperations in 13 patients, of which 7 were replacements and 8 were further repairs. There was one early and one late death.

***Mitral Valve Replacement.*** Current warfarin therapy in children is safe, with recent advances in INR monitoring that more often allow for a stable value in the range of 3 to 3.5.[44]

Recent series of mechanical MVR in the pediatric age group (including small patients)[29,45] suggest that MVR is performed with low operative mortality provided that the native annulus is large enough to accommodate the prosthesis in the anatomic position. Series of supra-annular implantations report elevated early and late mortality.[28,35] Freedom from second valve replacement is directly related to the age at initial MVR and to the size of the prosthesis implanted.[38]

## AORTIC VALVE DISEASE IN CHILDREN

### Definition

The study of aortic valve disease in children has usually been limited to those children born with an aortic valve abnormality. But in the present era, an increasing number of children are reaching adulthood with anomalies of the aortic root related to a birth defect or subsequent to a surgical procedure, and we decided to focus on this new developing field. Subaortic membrane stenosis, supravalvular aortic stenosis, Shone anomaly, infective endocarditis, and rheumatic valve disease, which are treated separately in other chapters, will only be briefly mentioned.

## History

Aortic valvotomy under direct vision was among the first congenital cardiac procedure to be reported as early as 1956.[46] Cabrol and Senning later paved the way to modern era aortic valve repair.[47,48] The introduction of the pulmonary autograft aortic valve replacement by Ross in 1967 has opened a new era of alternative replacement for those small children with no access to prosthetic valves.[49]

## Embryology

The mechanisms leading to the formation of the semilunar leaflets are not yet fully elucidated. It is believed that the aortic valve arise from three endocardial cushions appearing on the inner surface of the septated distal primitive outflow tract and that most of the malformations observed result from variable degree of fusion of the zone of apposition of these primitive leaflets. The fact that most valves (even unicuspid ones) present three interleaflet triangles seems to substantiate this theory. The few exceptions are represented by the cases of bicuspid and quadricuspid valves.[50,51] Intrauterine flow restriction through the aortic valve will accordingly model the size of the left ventricle. This seems to be a late phenomenon, because similar second trimester aortic lesions can result in either a normal-sized or a hypoplastic left ventricle.[52] The modeling of left ventricular size by flow through the aortic valve opens the potential for fetal aortic valve balloon dilatation to prevent the occurrence of hypoplasia of the left ventricle.[53]

## Pathophysiology

### CONGENITAL AORTIC VALVE DISEASE

Stenosis is the predominant feature of symptomatic congenital aortic valve disease in neonates and infants. With the fusion of the zone apposition between leaflets, the commissural area supporting the leaflets disappears, leading to a dome-like appearance of the valve. According to the number of zone of apposition between leaflets remaining open, the valve can be tricuspid, bicuspid, or unicuspid.[54] These valves often present considerable degree of fibrous dysplasia and nodular thickening. Due to the modeling of the heart components by flow during the fetal life, the more severe the obstruction, the smaller the ascending aorta.[55]

Bicuspid aortic valve is the most common morphological abnormality in patients who present as teenagers. The prevalence of aortic regurgitation (7 percent) or stenosis (3 percent) is low in these patients.[56]

### ACQUIRED LESIONS

A variety of congenital cardiac lesions are responsible for a deformity of one or more components of the aortic root.

***Tetralogy of Fallot and Pulmonary Atresia.*** Patients with right-to-left shunts and large collateral circulation as in pulmonary atresia have dilated aortic roots because their aorta has been subjected to high blood flow before definitive repair. Aortic root dilatation may cause central regurgitation by lack of coaptation of the leaflets related to dilatation of the sinotubular junction. This dilatation can progress even after surgical repair. Noninflammatory loss of smooth muscle cells with mucoid degeneration and fragmentation of the elastic fibers of the media has also been observed in the aortic wall of these patients.[57] It is yet unclear whether these abnormalities of the media are genetically inherited and related to their disorder or are induced by high flow in the aorta and/or cyanosis.[58]

***Ventricular Septal Defect–Related Regurgitation.*** This particular form of aortic valve regurgitation is seen in two particular forms of VSD: A perimembranous defect lies immediately underneath the interleaflet triangle between non- and right coronary cusps, whereas the doubly committed or infundibular defect corresponds to a lack of fusion underneath the right sinus of Valsalva and the crest of the septum; the defect is in this case strictly limited to the right cusp. Classically, the Venturi effect associated to the high velocity jet of restrictive VSD is responsible for the attraction of aortic leaflets into the VSD orifice.[59] Over time, the leaflet elongates and prolapses. At a later stage, the sinus dilates. Finally, the prolapsed leaflet may occlude the opening of the VSD. We believe that the lack of support to the right coronary cusp in doubly committed VSD is at least as important as the Venturi effect.[60] This would explain why the regurgitation is much less frequent in perimembranous VSDs.

***Iatrogenic Lesions: The Arterial Switch.*** All procedures involving the aortic root are prone to alter its geometry. In the arterial switch operation, the insertion of the coronary buttons in the neoaortic root at the level of the sinotubular junction may be responsible for regurgitation, as it may alter the ratio between sinotubular junction and the length of the cusp's free edge. It is disputed whether punch techniques, or any technique that inserts the buttons low into the sinuses, cause less distortion of the aortic root. There is a significant body of evidence suggesting that the neoaortic valve is structurally a pulmonary valve, therefore prone to dilation when exposed to systemic pressure. The physiopathology of the regurgitation is therefore not solely mechanical and related to the disruption of the sinotubular junction.[61]

***Subaortic Membrane.*** Valvular lesions observed in association with subaortic membrane are thought to be due to the systolic jet and vary from minimal damage to extensive fibrous proliferation extending to the ventricular surfaces of the leaflets, sometimes completely obstructing the interleaflet triangles.[62] Half of these patients present with some aortic regurgitation, even when the stenosis is responsible for mild gradients. The progressive incorporation of the valve in the fibrous proliferation of the membrane may ultimately lead

to severe valvar stenosis. In infants and children, valvular lesions are progressive, and surgery is recommended as soon as traces of regurgitation appear. This evolution might be slower during adulthood.[63]

***Supravalvar Aortic Stenosis.*** William's syndrome is found in half of the patients presenting with supravalvar aortic stenosis. The most frequently observed lesions are peripheral and supravalvar stenosis. In most instances, supravalvar narrowing is accompanied by considerable abnormalities of the aortic root.[64] The valve is bicuspid or stenotic in up to half the patients. Thickening and retraction of the sinuses, along with the fusion of the commissures to the sinotubular ridge is frequently responsible for various degree of coronary ostial stenosis. Left ventricular outflow tract obstruction is identified in as many as one fourth of the patients.[65] After operation, regurgitation due to distortion of the aortic root is not uncommon and we therefore favor the three-patch technique to repair these lesions, taking care to enlarge the sinotubular junction no more than the length of the free edge of the cusp.[66,67]

## Clinical Features

### EPIDEMIOLOGY

***Congenital Aortic Valve Disease.*** The exact incidence of aortic valve disease in children is difficult to evaluate, because most of the minor deformities of the valve will not become symptomatic for several decades. There seems to be male predominance in the disease.[68] A bicuspid aortic valve is observed in up to 2 percent of the general population, with males being affected four times more commonly than females.[56]

#### *Acquired Lesions*

**Pulmonary Atresia and Tetralogy of Fallot.** Almost 75 percent of repaired tetralogy patients present aortic root dilatation when they reach adulthood, accompanied by some degree of regurgitation; nevertheless, relatively few become symptomatic, and aortic catastrophe (rupture or dissection) is exceedingly rare.[69] Only 1 percent of the patients need surgery in the 20 years following their initial repair.[70,71] The progression of dilatation of the aortic root seems faster in patients becoming symptomatic than in those remaining asymptomatic.[72]

**Ventricular Septal Defect–Related Aortic Regurgitation.** Aortic valve prolapse is far more frequently encountered in doubly committed than in perimembranous VSDs. Eleven percent of the patients with perimembranous VSDs will have some aortic valve prolapse and a third of the prolapsing valves will cause more than trivial regurgitation. Up to two thirds of the patients with doubly committed VSD will show some degree of valve prolapse, with 40 percent of those having significant regurgitation. This incidence is even higher in men.[73,74] The severity of regurgitation invariably increases with time. Aortic regurgitation may appear after VSD closure even if the valve was not prolapsing before surgery. When present at the time of surgery, its progression seem to be halted by the closure of the VSD.[75,76]

#### *Iatrogenic Lesions*

**The Arterial Switch.** After an arterial switch operation, neoaortic regurgitation is very frequent but rarely significant. In 35 percent of the neonates regurgitation will appear, but only 2 percent of the total will need a reoperation for aortic insufficiency in the 10 years following the procedure.[77,78] Nonetheless, careful examination has revealed that as many as 25 percent of those having aortic regurgitation might have slow progression of their regurgitation over time.[79]

**Marfan Syndrome.** In early infancy, mitral pathology is responsible for most of the mortality of patients affected by Marfan syndrome. In childhood and adolescence, mitral valve prolapse and aortic dilatation have similar cumulative incidence. Four out of five Marfan patients reaching adulthood present aortic root dilatation, one in five with aortic regurgitation necessitating surgery.[16] Aortic dissection has only been exceptionally reported in patients with Marfan syndrome in the pediatric age group.[80] Aortic root involvement in the Marfan syndrome is discussed in detail in Chapter 82.

**Rheumatic Valve Disease.** In children and adolescents, the aortic valve and the mitral valve are, respectively, involved in 54 and 85 percent of the cases.[81]

**Infective Endocarditis.** The incidence of active infective endocarditis has increased in children in the last decade, mainly because of the improved survival of the patients at risk, such as hospitalized neonates and infants with indwelling catheters. Before 1970, the most important factor predisposing to endocarditis was rheumatic valve disease. Nowadays, the predominant predisposing factor has become the presence of congenital heart disease. The incidence is highest among patients with cyanotic heart disease, especially in patients who had operations for restricted pulmonary blood flow and those who had aortic valve replacement.[82]

## Clinical Features

Neonates and infants aged less than 3 months with aortic stenosis and reduced left ventricular function or duct-dependant systemic circulation are described to have critical neonatal aortic stenosis. At the time of ductal closure, if the aortic obstruction is severe, the neonate may be found in cardiovascular collapse. Later in the first year of life, the first symptoms may be tachypnea, poor feeding, and failure to thrive.

Most of the patients presenting after the age of 1 year with aortic stenosis or regurgitation will be asymptomatic.

Poor growth, angina, and syncope are found in less than 10 percent of the patients with aortic stenosis. In older patients, the most frequently encountered symptom is easy fatigability. Awareness of increased neck pulsation comes only in an advanced stage of aortic valve regurgitation.[83]

## Diagnostic Modalities

### EXAMINATION

In neonates presenting with critical aortic stenosis, poor pulses, hyperactive precordium, peripheral edema, and hepatomegaly may be noted. Although a murmur can be usually auscultated, the typical left sternal edge murmur radiating to the neck is present in only 20 percent of the patients.[84] In older children with aortic stenosis, the heave of the apical impulse can be detected on inspection and palpation. Visible bounding arterial pulses accompanying aortic valve regurgitation are more obvious with increasing severity of the disease.[85]

### ELECTROCARDIOGRAM

The electrocardiogram (ECG) is usually noncontributory to the diagnosis of neonatal aortic stenosis and can display signs of left or right ventricular hypertrophy. Under the age of 1 month, the predominant pattern is that of right ventricular hypertrophy. Older patients with severe aortic stenosis or regurgitation will show signs of left ventricular hypertrophy.[83,85]

### CHEST X-RAY

The chest X-ray of symptomatic neonates will invariably display cardiomegaly and, in 50 percent of patients, signs of pulmonary congestion. Older patients have a normal-size cardiac silhouette.[83,85] The presence of cardiomegaly with aortic stenosis is associated with a poor prognosis.[86]

### ECHOCARDIOGRAM

2-D echocardiography gives invaluable information about the morphology of the valve and the severity of the disease. Echocardiography should determine the morphology of the valve leaflets, their number, their quality, their mobility, and the presence of calcifications, fibrous nodules, or raphe. The commissures and hinge points have to be particularly scrutinized. The aortic root dimensions need to be measured at the level of the hinge points of the leaflets, of the sinuses and at the sinotubular junction and the ascending aorta. The evaluation of aortic regurgitation relies on the source of the jet, its orientation, and, if possible, the mechanism of the regurgitation. Dilatation of the aortic root, leaflet prolapse, and restrictive motion of the leaflets can all be responsible for aortic regurgitation. The short-axis view will better determine the opening of the valve and the source of the regurgitation, while the long-axis view will give details on the direction of the regurgitant jet, the coaptation area, and the eventual prolapse. In this latter view, the leaflet morphology should be carefully examined. Billowing of the body of the leaflet should be distinguished from true prolapse, in which the free edge falls below the level of the free edge of the facing leaflets. The coaptation area between the leaflets should be carefully assessed, as well as whether coaptation occurs adequately above the hinge points of the valve.

Pulse Doppler echocardiography allows the detection of even mild degrees of obstruction. Continuous-wave Doppler echocardiography provides a way to estimate the instantaneous pressure gradient through the valve by the simplified Bernoulli equation [pressure gradient = $4 \times$ (peak velocity)$^2$]. This calculated gradient slightly overestimates the peak-to-peak gradient measured invasively.[87] The evaluation of the transaortic flow is essential but has to be subjective. In this context, left ventricular function, especially shortening fraction and size of the left-to-right shunt at the interatrial or interventricular levels are key indicators. The presence of an open duct and the direction of the shunt at that level may give indication on the aortic pressure and may help with interpretation of the pressure gradient. Eventually, the severity of the obstruction is based on clinical judgment. The severity of aortic regurgitation is best assessed with pulsed Doppler echocardiography. The cross-sectional area of the regurgitant jet in the left ventricular outflow tract, and the holodiastolic abdominal aortic flow reversal seem to be better predictors of the degree of regurgitation than the length of the jet or the slope of the aortic regurgitation.[88,89] In the neonate, the dimensions of the left-sided chambers are evaluated, indexed for body surface area, and a $z$-score is determined. These measurements will help to determine the likelihood that the left heart will sustain the systemic circulation and, consequently, the patient's suitability for a biventricular repair. In particular, length of left ventricular cavity, mitral valve area, and presence of endocardial fibroelastosis should be recorded.[90–92]

Echocardiography is sufficient to elaborate the diagnosis of aortic valve disease in children. A thorough screening of associated anomalies is nonetheless mandatory.

### DIAGNOSTIC CARDIAC CATHETERIZATION

In the neonate, cardiac catheterization should be reserved for the evaluation of associated lesions. Beyond that age, catheterization will exceptionally help in the decision-making process in cases with borderline indications for surgery or valvuloplasty, or when there is a discrepancy between symptoms and echocardiographic findings.

### EXERCISE TESTING

Exercise testing is sometimes performed to assess patients with peak gradients inferior to 60 mm Hg in order to demonstrate ST changes, arrhythmias, or obtain precise evaluation

of the exercise capacity of adolescents with vague complaints of fatigability. Its usefulness in determining the indication for an invasive procedure remains to be established.

### MAGNETIC RESONANCE IMAGING

MRI is sometimes necessary and has been advocated for the evaluation of borderline left ventricle (LV) in critical aortic stenosis.[93,94] MRI allows calculation of LV volume and size irrespectively of the septal shift and interaction with the right ventricle. On the other hand, MRI is of limited help in delineating the anatomy of the valve.

## Medical Therapy

### CRITICAL NEONATAL AORTIC STENOSIS

The life-saving resuscitative measure in a neonate arriving in cardiovascular collapse is the administration of Prostaglandin $E_1$. Inotropic support and mechanical ventilation are required to treat heart failure. Thereafter, the evaluation of the child should enable the clinician to make the decision between a biventricular repair and a Norwood procedure. The largest study to date examining outcomes for critical aortic stenosis has identified the following parameters allowing prediction of survival with either of the two options: age, *z*-score of the aortic valve at the sinuses, grade of endocardial fibroelastosis, ascending aortic diameter, presence of moderate or severe tricuspid regurgitation, and *z*-score of the ventricular length.[90]

### INDICATION FOR SURGERY OR BALLOON VALVULOPASTY

Urgent intervention after adequate resuscitation is indicated for the infant presenting in shock or showing clinical or echocardiographic evidence of poor left-ventricular function. Patients presenting with high-peak gradients should be offered an early procedure, but there is increasing evidence that in asymptomatic patients, intervention can be delayed if they are submitted to a close follow-up.[95,96] The cut-off mean gradient for intervention has been usually set at 50 mm Hg, but this level has been decided arbitrarily. In children and adolescents, surgery or interventional catheterization will be recommended for symptomatic disease, repolarization or ischemic changes seon on ECG at rest or on exercise, and when the peak instantaneous transvalvular gradient is greater than 75 mm Hg. In aortic regurgitation, the presence of symptoms, left ventricular dysfunction (ejection fraction <50 percent) or an increase in left end-systolic diameters are indications for surgery.[97] In rheumatic valve disease, an operation is often required for the mitral component of the disease, while there is concomitant moderate aortic regurgitation. Valve repair in these circumstances seems rewarding with freedom from aortic valve dysfunction of 68 percent at 8 years.

### MEDICAL MANAGEMENT OF THE PATIENT WITH AORTIC VALVE LESION

There has been recent evidence that ACE inhibitor treatment in growing children with aortic regurgitation limits excessive increases in left ventricular mass and volumes.[98]

## Surgical Therapy

### APPROACH TO THE AORTIC VALVE

Many have advocated that a transverse aortotomy should be the preferred approach for aortic valve repair. In the pediatric population, this statement may not be necessarily true, because the main feature of aortic valve disease in the young age is valvar stenosis with its corollary, a small-sized ascending aorta. Therefore, the surgeon should not hesitate to perform an oblique aortotomy, extending the incision into the noncoronary sinus almost down to the level of the annulus in order to gain optimal exposure of the aortic valve and have, subsequently, the opportunity to enlarge the diminutive root and ascending aorta.

### AORTIC VALVE REPAIR

Once stay sutures are placed on the commissures or at 120 degrees from each other (where commissures should normally be positioned), one can appreciate the valve and the the eventual mechanism of regurgitation. In our experience, only the lack of mobility of the leaflets at their hinge points will preclude repair. Thereafter, the fused commissures are opened up to the aortic wall. The calcifications and fibrous nodes are resected. Local thickenings are shaved with caution. It has been our policy to remove thickening when it impairs the mobility of the leaflet or when it is obstructive per se, but to avoid "cosmetic" shaving of the cusps as we believe that it may promote further fibrosis and retraction. Tears from previous balloon dilatation are then closed directly or, if the regurgitation at this level caused a retraction of the cusp, by the adjunction of a glutaraldehyde-preserved autologous pericardial patch.

***Congenital Aortic Stenosis: Creation of Neocommissures.*** Congenital aortic stenosis often results from the partial or complete fusion of the zone of apposition of adjoining leaflets, followed by the involution of the apposed area. Therefore, the valve takes the appearance of a dome. Classical commissurotomy consisted of opening the roof of this dome-like structure, leaving the severed elements unsupported and thereby causing regurgitation. A typical bicuspid valve would be opened largely between its two main components, leaving the area of the raphe untouched. It has now been shown that tricuspid valve repair of congenital lesions give the best chances for long-term success.[99] Because the aorta is naturally small in these patients, it has been our policy to transform unicuspid valves into bicuspid valves and bicuspid valves into tricuspid ones by creating new commissures.[100]

The surgical instrumentation to achieve good valvotomy and commissuroplasty is very important. We use ophthalmic micro blades and specially modified ophthalmic tooth forceps (0.2-mm teeth).

The area of the potential commissure is identified and leaflets are opened in their direction, up to the aortic root wall. Calcifications and fibrous thickenings present in the raphe are resected. Stay sutures are placed at the highest point of the planned neocommissures, at the level of the planned sinotubular junction. Two separate patches of glutaraldehyde–preserved autologous pericardium are cut in a triangular shape. Each patch is then sutured with a continuous suture to the severed leaflet whether it corresponds to an opened doming valve or a previous raphe. The two patches are then secured together at the level where they join on the aortic wall. Both patches are trimmed if necessary in order to achieve the appropriate height and to leave the adequate tension on the free edge of the new leaflets. A continuous suture secures both patches to the aortic wall up to the previously positioned stay suture, marking the superior aspect of the neocommissure (Figs. 81-19 and 81-20).

***Cusp Extension.*** We leave the native tissue in place as long as mobility along the hinge points is preserved. As patch material, we favor autologous pericardium treated for 4 to 8 min in 0.625 percent glutaraldehyde and rinsed thoroughly. Three rectangular strips of pericardium patches are tailored as follows. The length of each patch is cut slightly longer than the free edge of the leaflet. The height of the patch should be calculated so that even with unequal leaflets, the newly recreated free edges are all at the same level. The patch extensions should not be redundant to avoid prolapsing, but should be high enough to achieve 4 to 5 mm of apposition in order to reduce the stress on the valve. The strips of pericardium are then sutured with a continuous suture to their respective leaflets, with the mesothelial face on the ventricular side and taking great care to avoid any gathering unless there is significant elongation of the free edge (as compared to the adjacent one). Stay sutures are positioned a few millimeters above the apices of commissures. It is at this stage that the length of the newly created free edge is set by cutting the redundant extremities of each patch. Theoretically, all three patches should have the same length, equal to the diameter of the sinotubular junction. In practice, this is done by bringing the three patches into a closed position with a temporary stitch at the center of the valve as would be done with a "Frater" apposition stitch. Then each adjacent half-free edge are apposed to give them the appropriate length and minimal tension, while maintaining the new commissures in their expected natural position, and the extremities of the strips of pericardium are cut. Each commissure is then recreated by suturing the two adjacent strips of pericardium to the aortic wall, progressing cephalad from the natural commissure. Great care should be taken to be perfectly aligned with the axis of the natural commissure. The suture is then passed outside of the aorta (Figs. 81-21 and 81-22A and B).

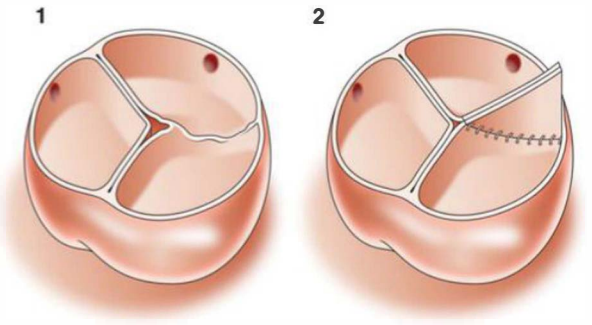



**FIGURE 81-20** Commissurotomy of a bicuspid valve and creation of a neocommissure leading to a tricuspid valve.

## SPECIFIC CONSIDERATIONS

***Bicuspid Valve.*** Beyond infancy, the dominant feature of bicuspid aortic valve will guide the surgical strategy. In pediatric patients, the bicuspid valve will almost always have

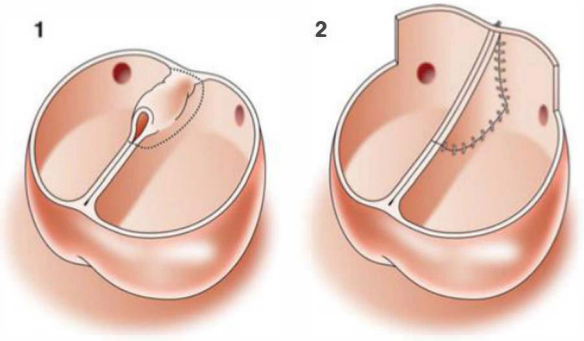



**FIGURE 81-19** Critical aortic stenosis: Commissurotomy of a unicuspid valve and construction of a neocommissure, with creation of a bicuspid valve.

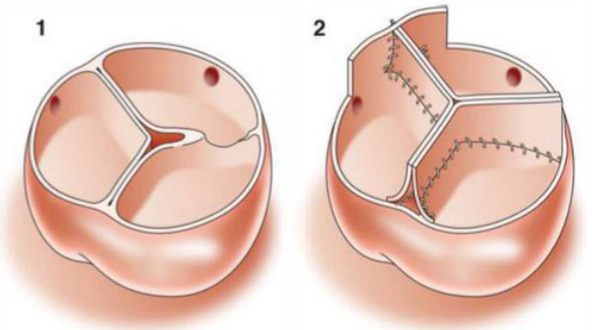



**FIGURE 81-21** Creation of a tricuspid valve by cusp extension with glutaraldehyde-treated autologous pericardium.

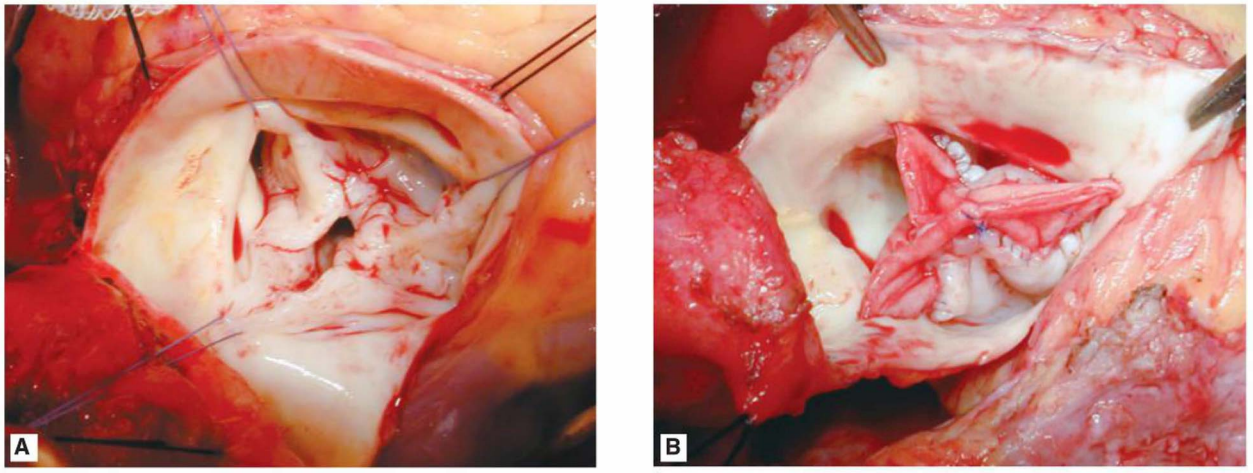



**FIGURE 81-22** Stenotic and regurgitant bicuspid valve. After tricuspidization and cusp extension.

some degree of stenosis; however, when the valve is predominantly regurgitant, the valve is most likely amenable to repair. The type of repair is guided by the size of the aortic root and the quality of the leaflet. If the root is of normal size and the leaflet thickened we would perform a tricuspidization of the valve by opening the raphe and performing a cusp extension. Exceptionally, in pediatric patients, we would find a very large aortic root with thin leaflets. The repair would be similar to the one performed in adults (second–fourth decade) with purely regurgitant bicuspid valve (Fig. 81-23). According to the anatomical finding, triangular resection of the raphe, free edge reinforcement with a PTFE suture, and subcommissural annuloplasty can be performed.[22,101]

***Ventricular Septal Defect and Aortic Regurgitation.*** A large number of techniques have been reported for this condition, but their application depends on the severity of the disease and the extent of prolapse. The primary lesion involves the displacement of the hinge point of the prolapsing leaflet through the VSD orifice, thereby limiting the effective height of right coronary cusp, with consequent reduction of the coaptation area and increasing the stress on its free edge. The free edge then elongates, the regurgitation increases, and secondary lesion appears on the adjacent cusps. We favor a technique with no patch, where the emphasis is on the repositioning of the hinge point toward the aortic lumen and the restoration of the normal height of the right coronary cusp together with triangular resection at the free edge whenever indicated.[60] In that case, to preserve the growth potential together with the fine mechanical properties and stress-relief ability of the commissure, a triangular resection is done at the midportion of the free edge (Fig. 81-24), or where it is most thickened (particularly if this allows maintaining the relationship with the other nodduli of Arantius). Through the aortotomy, pledgetted sutures are secured on the right ventricular edge of the VSD, passed through the mobilized leaflet hinge point (Fig. 81-25). Others have described a two-patch technique, using one patch for the VSD, and another for the dilated sinus.[102]

***Subaortic Membrane.*** Extensive resection of all extensions of the membrane is necessary. In the most severe cases, this necessitates peeling the surface of the interleaflet triangle and detaching finely the fibrous formation from the ventricular

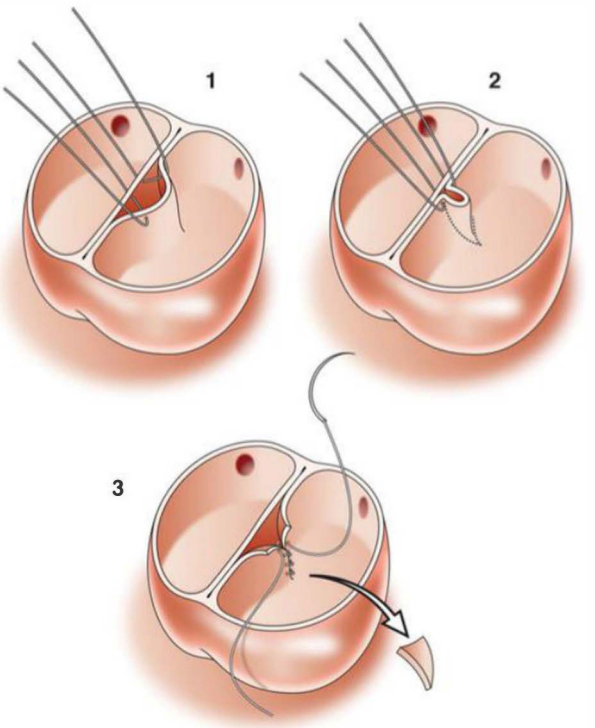



**FIGURE 81-23** Triangular resection at the free edge of a purely regurgitant bicuspid valve.

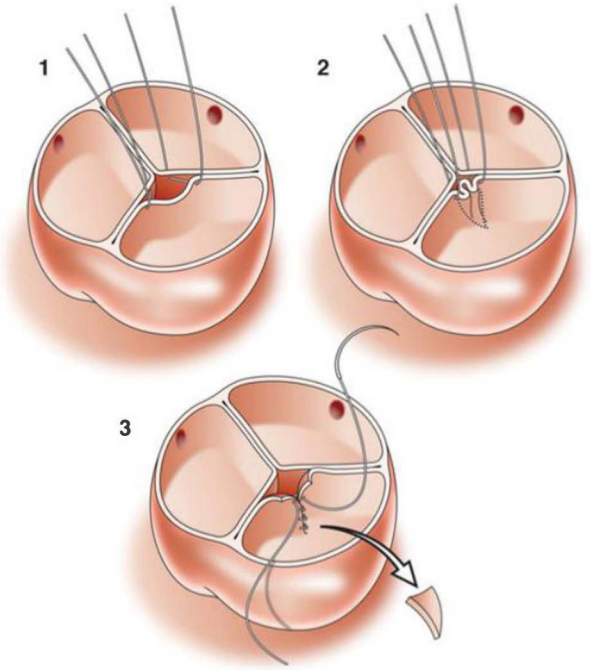



FIGURE 81-24 Method to calculate the width of the triangular resection at the free edge in a tricuspid valve.

aspect of the aortic leaflets. A systematic and aggressive myectomy of the interventricular septum away from the conduction has been shown to reduce the risk of recurrence.[62]

***Marfan Syndrome.*** Either mild or more severe, the aortic regurgitation in the Marfan syndrome in pediatric patients very rarely justifies surgical intervention in isolation. The treatment of the aneurysm of the sinuses and dilation of the sinotubular junction with or without aortic regurgitation is best dealt with by utilizing a valve-sparing procedure (see Chapter 82). The reimplantation technique should be favored over the remodeling technique.[103,104]

## AORTIC VALVE REPLACEMENT

The techniques of prosthetic valve replacement, Bentall procedure, and Ross procedure are essentially performed in infants and children as they are in adult patients. The main constraint is the limited size of the aortic root. For that reason, we avoid use of pledgetted or everting sutures to secure the valve in children, as these reduce significantly the effective annular diameter. Although the smallest mechanical valve available is a 17-mm prosthesis, we strive to insert at least one with a 19-mm diameter in order to reduce the need for reoperation. Techniques of annular enlargement are often necessary, either by incision of the commissure between left and noncoronary cusps and patching of the annulus onto the anterior mitral valve leaflet as described by Manouguian,[105,106] with a Konno procedure[107] or both.

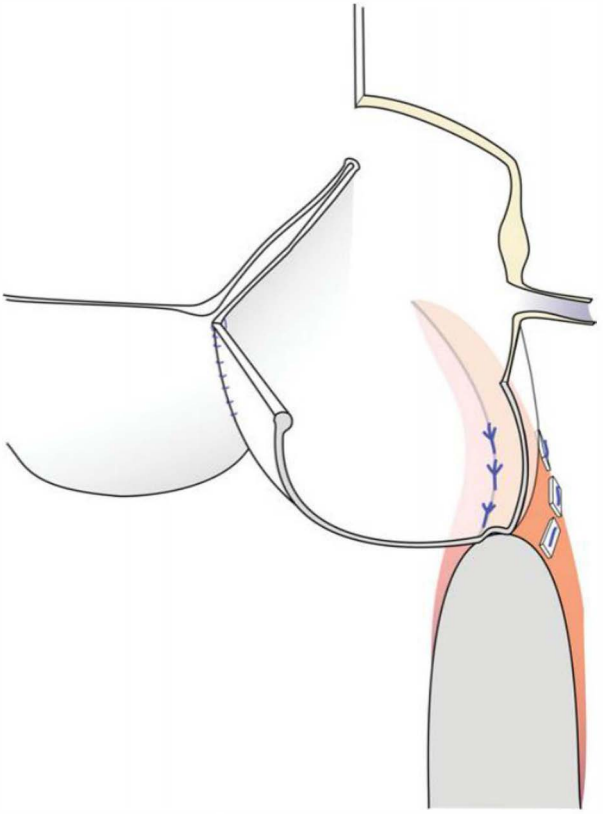


FIGURE 81-25 Repair of Infundibular VSD with aortic regurgitation: mobilization of the right coronary cusp. Fixation of the right coronary cusp to the crest of the defect at the point chosen to restore the height of the cusp. Triangular resection at the free edge.

The size constraint has in effect made the Ross procedure almost the only aortic valve replacement used in infants and small children. When performing a Ross procedure, it is essential to match the diameter of the aortic orifice with the one of the pulmonary autograft. In the presence of a small aortic orifice or a subaortic tunnel an aortoventriculoplasty as described by Konno (see Chapter 78) has to be performed. The latter actually is facilitated by excision of the autograft. When the pulmonary autograft is smaller than the aortic annulus, this has to be corrected by a subcommissural annuloplasty or even by a small triangular resection (reverse Konno or Manouguian) as well as an implantation very low into the left ventricle outflow tract. The correction of the mismatch with a large autograft cuff should be avoided at all cost[108] and, generally, the height of pulmonary autograft tissue (subpulmonary infundibulum) below the hinge point of the pulmonary cusps has to be kept to the strict minimum. An inclusion technique has been recommended as the procedure of choice when performing a Ross in the adults, but it is only exceptionally feasible in children because of the diminutive size of the aortic root.

## Outcomes

### BALLOON DILATATION VERSUS SURGERY

The outcomes of neonates with critical aortic stenosis is significantly worse, and the issue of congenital aortic stenosis in the neonatal period should therefore be addressed separately.[109] In this age group, the mortality seems independent of the type of procedure used, and ranges between 0 and 20 percent. The cause of death in this group is mostly related to the inadequacy of the left heart structures to fully sustain the systemic circulation.

Percutaneous procedures and surgical interventions relieve stenosis with fundamentally different modes of action, and this is reflected by the differences in the clinical consequences of both procedures. The inflation of a balloon angioplasty catheter will tear the valve in the plane of least resistance (mostly in the supple and mobile component of the valve), while classical surgical commissurotomy will open the fibrotic fused zones of apposition, leaving thickened leaflets with reduced mobility. Therefore, classically, balloon valvuloplasty will decrease the transvalvular gradient by 40 percent, while the surgical procedure will decrease it by 20 percent, but it will also be responsible for more aortic regurgitation. Avulsion of the valve with severe aortic regurgitation occurs after 5 percent of balloon dilatations.[110] Despite these differences, an extensive comparative clinical study performed in neonates failed to demonstrate significant difference between these procedures in their respective early mortality or long-term rate of reoperation. Thirty percent of the patients need a reoperation after 6 months and 50 percent after 5 years (Fig. 81-26). Preprocedural need for inotropic support, lower weight at valvotomy, and moderate-to-severe aortic valve regurgitation immediately after valvotomy were predictive factors for reoperation.[109]

In the older age group, the mortality is extremely low and, again, the results are remarkably comparable. The decrease in peak-to-peak gradient is around 50 percent after both types of procedures, and the transvalvular gradient and the severity of aortic regurgitation will gradually increase over time. The actuarial freedom from any reintervention is 80 percent at 7 years for surgical aortic valvotomy and repair,[111] while it is 54 percent at 10 years for the balloon valvuloplasty.[112]

Because of the similarity in results offered by interventional catheterization and surgery, the choice between the two procedures should depend on individual center preference and their relative expertise in both fields. However, all comparative studies to date have compared balloon valvuloplasty with classical techniques of surgical commissurotomy; we believe that with the more recently developed techniques of repair and new material becoming available, improved results with surgery will soon be evident.[100] It has been clearly demonstrated that the best results after balloon dilatation are achieved in patients with structurally tricuspid valves with fusion at the commissural level.[113] On the other hand, patients with truly bicuspid valves will not have a relief of their stenosis if the raphe is kept intact, and in this setting it is reasonable to think that surgery will achieve superior and more durable results. Therefore, irrespective of the age of the patients, we limit in our practice the indication for balloon dilatation to tricuspid valves with commissural fusion and annular *z*-value 0 or greater than 0, and prefer surgical correction for all remaining patients.

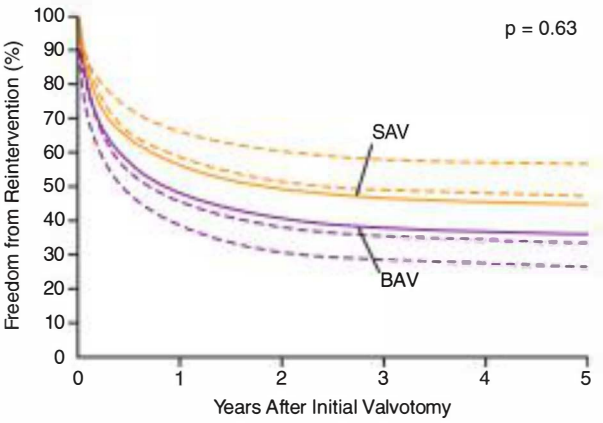



**FIGURE 81-26** Freedom from aortic valve-related reintervention stratified by type of initial aortic valvotomy (SAV, surgical valvotomy; BAV, balloon valvotomy), adjusted for differences in group characteristics. Solid lines represent parametric determination of continuous point estimates and dashed lines enclose 70 percent confidence interval (CI). (Reproduced with permission from McCrindle BW, Blackstone EH, Williams WG, et al. Are outcomes of surgical versus transcatheter balloon valvotomy equivalent in neonatal critical aortic stenosis? *Circulation* 2001 Sep 18;104(12 Suppl 1):I152–I158.)

### AORTIC VALVE REPAIR

Modern techniques of valve repair such as neocommissure reconstruction have only been introduced recently in the pediatric population, and the long-term results of valve repair in children can only be extrapolated from the adult experience and from the cusp extension techniques applied in rheumatic valves. Some authors have quoted a freedom from structural valve deterioration for cusp extension or cusp replacement with autologous pericardium of greater than 90 percent at 9 years after repair, without any need for anticoagulation.[114,115] Adults with biscuspid valve repair *without* cusp extension have a 7-year freedom from reoperation of 84 percent.[101]

Valve-sparing procedures can successfully be performed in children with good midterm outcome.[103] At the RCH, Melbourne, we have introduced the tricuspidization of bicuspid aortic valve with cusp extension in 1999 and 2005[116] to reduce the residual gradient after repair. The freedom from reintervention is 66 percent at 7 years in this series.[111] Two deaths occurred in this series and may have been linked to coronary obstruction. This has led us to limit the usage of this technique to aortic roots with symmetrical sinuses and well-positioned coronary ostia.

Recurrence of regurgitation is rare after valve repair for VSD-related aortic regurgitation, and 15-year freedom from reoperation as high as 81 percent has been reported.[117] Long-term valve function depends greatly on the regurgitation grade at the time of the repair. All authors insist on early intervention as soon as traces of aortic regurgitation become evident during follow-up.

The aortic regurgitation associated with subaortic membranes regresses in the majority of operated cases, especially when aggressive resection of all the proliferative tissue is undertaken.[62]

## AORTIC VALVE REPLACEMENT

***Bioprosthesis.*** The use of bioprostheses has been abandoned in children due to their unacceptable rate of calcification and degeneration leading to reoperation in 75 percent of the patients within 5 years.[118] They should only be considered as a last resort in patients in whom anticoagulation is strictly contraindicated, and for those patients who are not candidates for a Ross procedure, such as female patients of childbearing age.

***Mechanical Valves.*** The operative mortality of children undergoing a mechanical valve replacement is higher than for adult patients (between 2 and 13 percent), mainly as a result of concomitant risk factors such as previous surgery, associated conditions necessitating repair, and poor ventricular function.[105,119] In this age group, major bleeding and thromboembolic events are remarkably rare, with an estimated linearized rate of 0.3 percent per patient year for each of these complications. The events are usually due to lack of compliance with anticoagulation treatment in the adolescent age group.[120,121] Ten-year freedom from reoperation is approximately 92 percent in this age group. The 10-year survival rate is around 75 percent.[119,122] Some authors have pointed out that congenital patients may be prone to late pannus formation in the subvalvar area and that they might be more susceptible to late valve failure than their adult counterpart.[123]

***Homografts.*** The 10-year freedom from tissue failure for aortic valve replacement with homografts is 62 ± 3 percent in large series of adult patients. The incidence of valve deterioration is higher in the adolescent and in the young adult, and is highest in infants; these data preclude liberal use of homografts in this age group.[124] The risk of requiring reoperation after allograft aortic valve replacement is greater than 50 percent in the 3 years following implantation when performed in children aged less than 3 years.[125]

***Ross Procedure.*** Reported mortality for Ross procedure in children usually varies between 0 and 6 percent.[126,127] The advantages of the Ross procedure are obvious in children. The procedure allows the best anatomical restoration of the left ventricular outflow tract, with no residual gradient, no need for anticoagulation, and can be performed in all age groups. It has also been demonstrated that the growth of the autograft parallels somatic growth.[128]

Comparative retrospective studies seem to underline the superiority of the pulmonary autograft when considering both survival and valve-related complications.[123,129] The actuarial risk of autograft failure in pediatric patients is around 12 percent at 2 years; 40 percent of patients will have equal or greater than moderate regurgitation at 6 years and almost all patients will eventually demonstrate a neoaortic root $z$-score greater than 4.[130]

The Ross procedure can also be performed for aortic rheumatic valve disease, but long-term results are very disappointing and its use should be avoided in this particular subgroup of patients.[131]

The Ross procedure may be the only valve replacement procedure in pediatric patients, especially neonates and infants, but it is not the only surgical alternative.

Despite its apparent ideal characteristics, the Ross procedure may not be the panacea to offer to all children. Geometric mismatch between the aortic and the pulmonary root seem to be responsible for a high rate of autograft failure, especially when the procedure is performed for aortic valve regurgitation.[108] There is an increasing concern that all autografts implanted as a root are subjected to progressive dilatation, and it is not yet known how many will need a reoperation for neoaortic regurgitation in the future.[132] Studies have reported that, at 5 years, 25 percent of autografts will present with more than mild regurgitation.[127]

We therefore believe that aortic valve repair should be attempted in all circumstances where feasible, especially in infants and children. It is likely that a number of these repairs will fail with time, especially those involving extensive reconstruction with pericardium. In addition, because geometric mismatch between the pulmonary and the aortic root predisposes to the autograft failure after a Ross procedure, we offer primary valve repair for all infants, in the hope that it might allow for near-normal growth of the aortic root; the Ross procedure can then be performed at a later age, when inclusion or other means of reinforcement of the autograft can be used with more favorable long-term results. When the primary concern is aortic regurgitation, the rate of autograft failure is substantial. These lesions seem the best suited for repair, and we strongly recommend repair in these situations. When the lesion is predominantly stenotic and the annulus is small, a Ross procedure is indicated.

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82

# Cardiac Surgical Intervention in Pediatric Patients with Connective Tissue Disorders

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**KEY CONCEPTS**

- Thoracic aortic aneurysm syndromes are due to genetic disorders inherited as autosomal dominant traits with reduced penetrance and incomplete expression. Hence, clinical phenotype is complex and highly variable with often no genotype-phenotype correlation.
- Altered TGF-β signaling and proteolytic metabolism involving the entire aortic wall are now challenging old pathophysiologic models by which aortic aneurysms were solely caused by extracellular matrix structural protein deficiency in the media.
- Indications for surgery are still mainly based on aortic diameter as well as aortic growth rate and family history of early rupture/dissection. However, efforts are made to identify circulating markers associated with early complications to guide risk stratification.
- Surgery is the only treatment that can modify the natural history of pediatric patients with thoracic aortic aneurysm syndromes. Although promising, medical treatment has not yet been validated.
- Aortic valve-sparing root replacement (AVSRR) is currently the favored surgical approach, whereas the Bentall operation should be reserved for patients with acute aortic dissection, unrepairable leaflet damage, or failed AVSRR. Early and midterm results of AVSRR in pediatric patients are excellent and comparable to those obtained with composite valve graft root replacement. Long-term event-free survival in this particular group of patients has yet to be assessed.

## INTRODUCTION

Arterial aneurysms in children are typically due to a genetic abnormality and represent the most lethal clinical feature observed in the setting of connective tissue disorders. The most prevalent sites of vascular catastrophe in these young patients are the aortic root and the ascending aorta.

Pediatric aortic surgery for patients affected by connective tissue disorders is a rapidly evolving field. As a better understanding of the underlying aortic wall pathology is achieved, diagnosis is improved and treatment objectives, surgical indications, operative strategies, and expected outcomes change.

Although over the past 20 years treatment goals have shifted from life-saving measures to preemptive surgery in the hopes of achieving long-term event-free survival, risk stratification and surgical decision-making are still imperfect. Surgical indications are mostly based on clinical diagnosis, aneurysm size, and family history. The absence of biomarkers predictive of malignant clinical course, along with the lack of a large body of data on natural history and true long-term treatment outcomes impact our ability to predict the aortic size at which vascular complications may occur in each patient. Aortic root pathology and aneurysms are described in detail in Chapter 39. We will hereby expand on the topic by focusing on patients in the pediatric age group.

## PATHOPHYSIOLOGY

Thoracic aortic aneurysm in the setting of connective tissue disorder is a syndromic disease with multiple, complex phenotypes. Within each disease, clinical heterogeneity due to mosaicism, incomplete penetrance, and age-dependence of the phenotype is common. These features account for the lack of a complete understanding of the pathophysiology underlying thoracic aneurysm syndromes.

Historically, pathogenetic models of ascending aortic aneurysm were centered on abnormalities of structural protein of the extracellular matrix as a cause of connective tissue weakness leading to aneurysm formation. The near-uniform finding of elastolysis in the media ultimately leading to cystic medial necrosis was the anatomic hallmark. Along these lines of reasoning, Marfan syndrome was thought to be exclusively caused by deficiency of the microfibrillar protein fibrillin-1, Elhers–Danlos vascular type caused by qualitative and/or quantitative alteration of collagen type III, and bicuspid aortic valve with aneurysm caused by altered vascular collagen production.

Recent insights gained while studying Marfan syndrome highlighted the importance of cytokine dysregulation and, in particular, the potential role of TGF-β in the pathogenesis of aortic aneurysms. Deficiency of fibrillin-1 would lead to failed sequestration of TGF-β in the matrix and hence deregulated activation of and signaling by TGF-β in arterial wall tissues. TGF-β signaling, in turn, would result in the activation of proteolytic enzymes such as thrombospondin-1 and matrix metalloproteinases, causing extracellular matrix degeneration and loss of elastic properties ultimately leading to aneurysm formation.

Even though the etiology of most aortic aneurysm syndromes is still largely unknown, convincing evidence of amplified TGF-β signaling in the aortic wall has also been observed in patients with bicuspid aortic valve and aneurysm and Loeys-Dietz syndrome.[1,2] In patients with Loeys-Dietz syndrome, mutations in the genes for either TGF-β receptor 1 or 2 are associated with increased downstream TGF-β signaling within the arterial media; this in turn leads to increased collagen synthesis, loss of elastin content, and elastic fiber disarray. The ultrastructural end-result is an extremely thin aortic wall that has decreased elastic properties and is prone to dilatation and dissection.

Recent studies on aneurysm progression strongly emphasize molecular events taking place in the adventitia during aneurysm formation, challenging the long-held assumption that aneurysms originate from a disease processes harbored in the media.[3] This new concept by which the adventitia assumes an active role in aneurysm formation is supported by the old observation of maintenance of wall integrity following endarterectomy and the fact that patients with failed elastogenensis and generalized medial disorganization will typically not manifest aneurysm formation.[4]

Currently, the pathogenesis of ascending aortic aneurysm in pediatric patients is conceived as the final result of a complex and yet incompletely understood interplay between signaling pathways, most likely orchestrated by altered TGF-β signaling throughout the entire aortic wall. Alteration of specific matrix proteins in the arterial wall may be the initiating event as well the end-result of this process.

## CLINICAL FEATURES

### Marfan Syndrome

Marfan syndrome is an autosomal dominant disorder with complete penetrance but variable expression that affects 2 to 3 in 10,000 individuals.[5] In approximately 25 percent of patients, the disease is due to a de novo mutation.[6] Cardinal clinical findings include annuloaortic ectasia, dislocation of the ocular lens, and long bone overgrowth (Table 82-1).

Clinical course is heavily dependent on age of presentation. The infantile form of Marfan syndrome has an early onset of aneurysm formation and is distinguished by an aggressive clinical course.[6–9] Yet the aggressiveness of the clinical course is usually dominated by mitral valve disease, which stands as the leading cause of morbidity and mortality in this particular age group.[10] In fact, aortic catastrophes are exceptionally rare in Marfan patients younger than 12 years of age, almost irrespective of the degree of aortic dilatation; in this age group, aortic rupture/dissection occurs mainly in the case of giant aneurysms, often following progressive aortic insufficiency.[6,7,9,11,12] Rupture of an enlarged aortic root is instead the leading cause of death in adolescents.[5,13,14] In these patients, aortic regurgitation rarely begins at an aortic diameter <6 cm, but many experience dissection at significantly smaller root diameters.[15]

In children, determinants of aortic complications are aneurysm absolute size and growth rate, and family history of premature dissection.[5] In young patients, the average size of the aortic root at the time of dissection is 5.1 cm and when aortic diameter exceeds 6 cm, there is a 4 to 8-fold increase in the cumulative risk of rupture.[16–18] Also, if the aortic root expands at a rate greater than 15 mm/year, aortic dissection is more common.[14] Finally, family history of aortic complications at relatively small diameters suggests the presence of a particularly frail aortic wall and a greater propensity for premature aneurysm rupture.

### Loeys–Dietz Syndromes

Loeys–Dietz syndrome is an autosomal dominant connective tissue disorder caused by mutations in the genes encoding for transforming growth factor β receptors 1 and 2 (*TGF-β*). It is characterized by premature ascending aortic aneurysm and dissection at small aortic diameters and at younger age compared with any other connective tissue disorder (Table 82-1 and Fig. 82-1).[19]

Clinical expression is variable with features that, on the mild end of the spectrum, are similar to those of Marfan syndrome.[20,21] On the opposite end of the clinical spectrum, is a complex phenotype in which aortic dissection or rupture

**TABLE 82-1: Characteristic Features of Aortic Aneurysm Syndromes in Children**

| | Aortic Involvement[a] | Earliest Presentation[b] | Dissection in Childhood/ Adolescence | Dissection at Small Diameter | Life Expectancy[c] following Repair (Years) | Systemic Features |
|---|---|---|---|---|---|---|
| Marfan syndrome | Root | Infancy | Possible | Possible | 70 | Ectopia lens<br>Skeletal deformities |
| Loeys–Dietz syndrome | Root | In utero | Likely | Likely | 37 | Hypertelorism<br>Bifid uvula<br>Arterial tortuosity |
| Ehler–Danlos syndrome | Ascending aorta | Adolescence | Probable | Likely | 48 | Facial appearance<br>Translucent skin<br>Visceral rupture |
| Bicuspid aortic valve | Ascending aorta | Childhood | Unlikely | Possible | Undefined, most likely similar to the general population | None |

[a]Most prevalent site of aneurysm occurrence.
[b]Earliest presentation of aortic aneurysm/dissection/rupture.
[c]Life expectancy in treated patients.

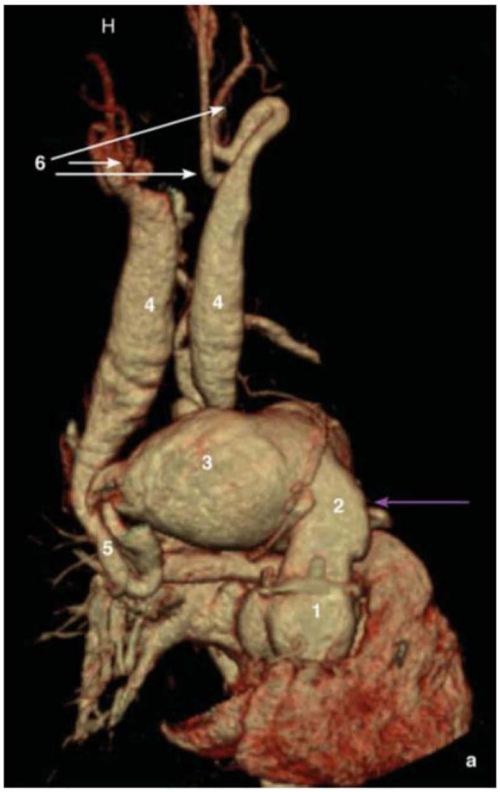



**FIGURE 82-1** Severe aortic pathological findings in a 2-year-old child with Loeys–Dietz syndrome. Three-dimensional computerized tomographic reconstruction, posterior view. This child experienced an acute type A aortic dissection requiring replacement of a portion of the ascending aorta with an interposition graft (2). Of note is the very prominent vascular tortuosity (5) and the diameter of the epiaortic vessels (4). The patient required total arch replacement and valve-sparing root replacement at 5 years of age. (Image courtesy of Dr. Eloisa Arbustini, IRCCS Foundation Policlinico San Mateo, Pavia, Italy.)

commonly becomes apparent in early childhood.[19] Two main syndromic pictures have been described. Patients with Loeys–Dietz syndrome type I are characterized by the clinical triad of hypertelorism (90 percent), bifid uvula and/or cleft palate (90 percent) (Fig. 82-2) and generalized arterial tortuosity with aneurysm formation (84 percent). None of these clinical features are present in patients with Marfan syndrome and are key for clinical diagnosis. Ninety-eight percent of these patients develop aortic root aneurysm early in life.[2] Patients with Loeys–Dietz syndrome type II lack these craniofacial features (though bifid uvula may be present) and



**FIGURE 82-2** Typical craniofacial features of child with Lowys–Dietz syndrome type 1. (Reproduced with permission from Williams JA, Loeys BL, Nwakanma LU, et al. Early surgical experience with Loeys-Dietz: a new syndrome of aggressive thoracic aortic aneurysm disease. *Ann Thorac Surg* 2007;83(2):S757–S763.)

have at least two manifestations of the Ehlers–Danlos syndrome (easy bruising, characteristic facial appearance, wide and atrophic scars, joint laxity, translucent/velvety skin, visceral rupture) with no type III collagen biosynthesis deficit. Patients with Loeys–Dietz syndrome type I endure a more severe cardiovascular course than those with Loeys–Dietz type II. Importantly, more severe craniofacial abnormalities are related to worse cardiovascular outcomes among type I patients.[2]

The most important feature of Loeys–Dietz syndrome is that aneurysms commonly dissect at sizes smaller than those seen in patients with Marfan syndrome. In children with Loeys–Dietz syndrome, aortic dissection often occurs at diameters well under 5.0 cm.[2,22] It is imperative therefore to normalize aneurysm size to age and body size ($z$-score) to guide risk stratification for aortic complications and appropriately plan for surgery.

## Vascular Ehlers–Danlos Syndrome

Vascular Ehlers–Danlos syndrome is a rare autosomal dominant disorder, characterized by extreme fragility of the connective tissue leading to arterial and hollow organ rupture as well as anastomotic complications following surgical intervention (Table 82-1). Dissection and rupture of large arteries are the hallmark of this disease. The estimated prevalence of all Ehlers–Danlos syndromes (six subtypes) ranges between 1:10,000 and 1:25,000, and the vascular type represents about 5 to 10 percent of all cases.[23] Mutations in the COL3A1 gene coding for type III procollagen (mainly located in skin, vessel walls, and hollow organs) cause the phenotype, with no genotype–phenotype correlation.

Cardinal clinical findings are: facial appearance (emaciated face with prominent zygomata and sunken cheeks, thin nose and undefined lip edges), thin skin with visible veins and easy bruising, rupture of arteries, gravid uterus or intestine.[23,24] Diagnosis is often missed, with approximately 75 percent of patients presenting in adulthood with major vascular complications.[25] Median survival is 48 years and the primary cause of death is arterial dissection or rupture (80 percent), often involving the thoracic aorta.[24,25] Although vascular complications are rare in early childhood, patients with vascular Ehlers–Danlos syndrome have a 25 percent risk of experiencing a major vascular complication by the age of 20 years.[23–25] As for virtually all the orphan diseases, diagnosis is often missed until severe complications occur.

## Congenitally Bicuspid Aortic Valve

Congenitally bicuspid aortic valve is a common cardiac anomaly that clusters in families and has a prevalence of 0.5 to 2 in 100 individuals among the general population.[26–28]

There are three major types of aortic aneurysms associated with a congenitally bicuspid aortic valve. The most common is the fusiform aneurysm of the ascending aorta (Table 82-1), which begins above the sinotubular junction and terminates proximal to the innominate artery. The most rare type involves the aortic root and extends below the sinotubular junction, resembling aneurysms found in patients with Marfan syndrome. An intermediate type may also be observed.

In patients with a congenitally bicuspid aortic valve, aortic dilatation is a well-known phenomenon and its evolution has been recently characterized since the early phase. In these patients, aortic dilatation begins by 1 year of age and steadily progresses throughout childhood. About one-third of the patients with an initially normal aortic size develop an ascending aortic aneurysm by adulthood. Predictors of larger ascending aortic aneurysm and aortic root diameter are age and smaller body surface area, whereas valve gradient and right–left valve fusion have been found to be predictors of more rapid aneurysmal growth in the ascending aorta.[29] Although aortic dissection is more likely in patients with a dilated aorta, in some families dissection has been described at diameters under 5.0 cm similarly to other thoracic aortic syndromes.[11,30] Again, risk factors for malignant course are mostly unknown.

# MEDICAL (NONSURGICAL) THERAPY

Current nonsurgical management of thoracic aortic syndromes includes serial aortic imaging along with echocardiographic studies and use of oral medications aimed at reducing mechanical stress on the aortic wall.

Imaging of the entire aorta and large vessels is performed at diagnosis and yearly thereafter unless the clinical course of the disease warrants a more frequent reassessment computed tomography (CT or MR angiography). Similarly, echocardiograms are obtained at diagnosis and subsequently every 6 months unless otherwise indicated by severity and progression of aortic valve insufficiency. Following surgery, ventricular and aortic valve function are assessed to establish a baseline for subsequent evaluations performed at 1-month follow-up and yearly thereafter.

β-adrenergic blockers (e.g., atenolol) have been a pharmacological cornerstone in the treatment of Marfan syndrome for years, only substituted by calcium channel blockers or angiotensin receptor blockers (ARBs) when β-blocker intolerance occurs (mostly due to asthma, depression, fatigue). β-blocker agents may stabilize aortic root growth, although this has not been a consistent finding.[31] As murine models of Marfan syndrome showed the key role of TGF-β overexpression in aortic root enlargement, ACE-inhibitors (e.g., perindopril) and ARBs (e.g., losartan), known to have intrinsic anti-TGF-β activity, were tested in small cohorts of Marfan patients.[32] Although observed reduction in aortic root enlargement raised hope for medical treatment for this syndrome, the small sample of the patient population investigated and the relatively short study time posed some legitimate concerns on the beneficial effect of anti-Angiotensin II medications, especially when the underlying genetic variability is taken

into account. Mechanisms of action, relative potency, and duration of protection with each class of medication remain to be elucidated. The lack of circulating markers to assess short-term efficacy also affects the ability to individualize treatment. While awaiting final results of randomized clinical trials comparing Losartan with β-blockers in children and young adults with Marfan syndrome, β-adrenergic blockade remains as first line of treatment in patients with ascending aortic aneurysms.

It cannot be overemphasized that, when size criteria are met, surgical intervention is warranted. Despite the fact that medical therapy is promising in the treatment of Marfan syndrome and possibly of other aortic aneurysm syndromes, only surgery is able to modify the natural course of the disease.

## INDICATIONS FOR SURGERY

Due to clinical heterogeneity, individualized management of children with aortic root aneurysms is paramount. In particular, differentiated size criteria for operative intervention among the various syndromes is key, and its importance can never be overemphasized (Table 82-2).

In children with Marfan syndrome, Elhers–Danlos type IV, or with bicuspid aortic valve, timing for aortic repair is mostly based on the absolute size of the aneurysm and surgery is recommended when the diameter reaches 5 cm.[5,11,33–36] Aneurysm growth rate exceeding 1 cm/year, progressive aortic insufficiency and familial history of premature aortic dissection warrants earlier intervention (Table 82-2).[5,11,33–35] In children younger than 12 years of age, indications for surgical intervention are the finding of "giant aneurysms" (those that satisfy the adult criterion for intervention), rapid enlargement (>1 cm/year), and progressive aortic insufficiency (Table 82-2). In these young patients, we do not utilize *z*-scores as indicators for surgery, as dissection is rare irrespective of aortic dilation.[6,7,9,11,12]

Given their propensity to dissect even at small aortic diameters, patients with Loeys–Dietz syndrome require a completely different treatment algorithm. The algorithm currently in use at the Johns Hopkins Hospital is reported in Table 82-2.[37] In young children, surgery should be considered when aortic size exceeds the 99th percentile or when a diameter of 3 to 3.5 cm is associated with severe craniofacial deformity. However, every effort should be made to stabilize aneurysms with medical therapy and defer surgery until the aortic annulus is greater than 18 mm, which will allow the use of a large enough graft or prosthesis to accommodate growth into adulthood. Yet a different clinical approach is used for adolescents, who fall under the same algorithm utilized for adults.

## SURGICAL INTERVENTIONS

Surgical options available for the treatment of aortic root aneurysms in the pediatric population are manifold: composite valved tube graft (mechanical vs biological), aortic homograft, and aortic valve-sparing root replacement (AVSRR).

At present, valve-sparing procedures should be considered as the first-line choice in children with an aortic annulus greater than 18 mm, undamaged valvular leaflets, no evidence of acute aortic dissection and no need for mechanical mitral valve replacement. If simultaneous mitral valve

**TABLE 82-2: Surgical Indications for Pediatric Patients with Aortic Aneurysm Syndromes**

| | Children (<12 years) | Adolescents |
|---|---|---|
| Marfan syndrome | Aortic root/ascending aorta >5.0 cm<br>Aortic root/ascending aorta <5.0 cm if:<br>1. Rapidly expanding aneurysm (>1 cm/year)<br>2. Progressive aortic insufficiency (AR > mild)<br>3. Family history of premature aortic dissection (<5 cm)<br>4. Large root at the time of intervention on the mitral valve | Same as children |
| Loeys–Dietz syndrome | Severe craniofacial features:<br>1. Aortic root *z*-score <3.0<br>2. Rapidly expanding (>0.5 cm/year)<br>3. Annulus ≥1.8 cm (if possible)<br>Mild craniofacial features:<br>1. Aortic root *z*-score >4.0<br>2. Rapidly expanding (>0.5 cm/year) | 1. Aortic root diameter >4.0 cm<br>2. Rapidly expanding (>0.5 cm/year) |
| Ehler–Danlos syndrome | Similar to Marfan syndrome | Same as children |
| Bicuspid aortic valve | Aortic root/ascending aorta >5.0 cm<br>Aortic root/ascending aorta <5.0 cm if<br>1. Rapidly expanding (>1 cm/year)<br>2. Need for aortic valve surgery (aortic diameter >4.5 cm) | Same as children |

repair is needed, it is standard practice to commence repair with the mitral valve. If the mitral valve needs to be replaced, then a Bentall procedure is a more sound option. Also, valve-sparing surgery in the setting of acute aortic dissection is not unreasonable, although technically more challenging challenging. However, the acuity of the clinical picture along with the many variables that may severely impact surgical outcome (coagulopathy, malperfusion, hypothermia) raise the question as to whether this operation is advisable in such a context. Finally, the presence of a congenitally bicuspid aortic valve is not a contraindication to a valve-sparing operation unless leaflet stress lesions, calcification, or severe and asymmetric prolapse make the leaflets unrepairable.

A composite mechanical-valve graft is favored in the presence of acute aortic dissection, aortic leaflets with unrepairable stress lesions (elongation/fenestration) or grossly asymmetric valve prolapse. A composite tissue–valve graft is indicated in young patients unsuitable for valve-sparing procedures, who cannot undergo anticoagulation or wish to become pregnant.

Homografts are still used in the setting of a small annulus (<18 mm) if the aortic valve cannot be preserved (Table 82-3), but durability is disappointing and therefore their use is becoming obsolete.

Although intuitive, it is worth mentioning that pulmonary valve autotransplantation (Ross procedure, see Chapter 78) is formally contraindicated in the setting of connective tissue disorders due to the intrinsic weakness of the pulmonary root.

Composite valve graft aortic root replacement is described in detail elsewhere in this textbook; we detail to follow the surgical technique currently in use at the Johns Hopkins Hospital for AVSRR as it is applied to pediatric patients with aortic root aneurysms.

## AORTIC VALVE-SPARING ROOT REPLACEMENT

It is now generally accepted that, in the setting of connective tissue disorders, aortic valve reimplantation techniques (David-type procedures) offer superior long-term anatomic and functional results when compared with remodeling of the aortic root (Yacoub operation). We therefore preferentially perform aortic valve reimplantation when AVSRR is indicated in pediatric patients. The Valsalva Gelwave graft is o ur graft of choice in pediatric patients in whom a graft of diameter equal or greater than 24 mm is chosen. Criticism against grafts with prefabbricated pseudosinuses has focused on the inability to tailor the prosthesis to individual patient anatomic variability; however, we have found these grafts are easy to use and adequately suit the needs of the vast majority of our pediatric patients.[38,39] Furthermore, most pediatric patients with connective tissue disorders will present for surgical intervention with annular diameter similar to that of an adult. This is important, as the fallback option in these patients is a mechanical prosthesis, available in diameter of greater than 18 mm.

After induction of general anesthesia, anatomy and function of the aortic root and ascending aorta are reviewed via transesophageal echocardiogram. Diameters of aortic annulus, sinuses, sinotubular junction, and ascending aorta are remeasured and the function of the aortic valve reassessed.

Access is obtained via median sternotomy and the pericardium is opened longitudinally. After systemic heparinization, the aorta is cannulated at the most distal part of its ascending segment and bicaval cannulation performed. Myocardial protection is obtained by means of cold blood cardioplegia infusion and topical ice-cold saline. Also, the left ventricle is vented through the right superior pulmonary vein. To prevent air embolism, the surgical field is flooded with carbon dioxide.

Before accessing the aortic lumen, the right atrium is routinely opened and the presence of a patent foramen ovale ruled out. The ascending aorta is then transected just above the sinotubular junction and dissected free from the pulmonary artery first and then down to the level of the annulus (Fig. 82-3A).

The aortic valve is inspected and the aortic annulus meticulously sized. Particular attention is paid to pliability and integrity of the cusps as well as the anatomic position of the coronary arteries.

We simplify the choice of the aortic graft by determining the optimal sinotubular junction diameter (the one that allows proper leaflet coaptation). Stay sutures are placed at each commissure to retract the aortic valve apparatus and obtain adequate leaflet coaptation. Valve continence is repetitively tested until the size of the sinotubular junction that

**TABLE 82-3: Choice of Surgical Technique for Aortic Root Replacement in Children with Connective Tissue Disorders**

| AVSRR | Bentall | Homograft |
|---|---|---|
| 1. Elective cases<br>2. Pliable and symmetric leaflets<br>3. Annulus >18 mm<br>4. Aortic valve needing straightforward repair techniques | 1. Dissection<br>2. Prominent leaflet elongation or fenestrations<br>3. Need for concomitant mitral valve replacement (mechanical) | AVSRR not suitable and:<br>1. Small annulus not amenable to enlargement (infants and very small children)<br>2. Contraindication to anticoagulation (young women of childbearing age) |

AVSRR, aortic valve-sparing root replacement.

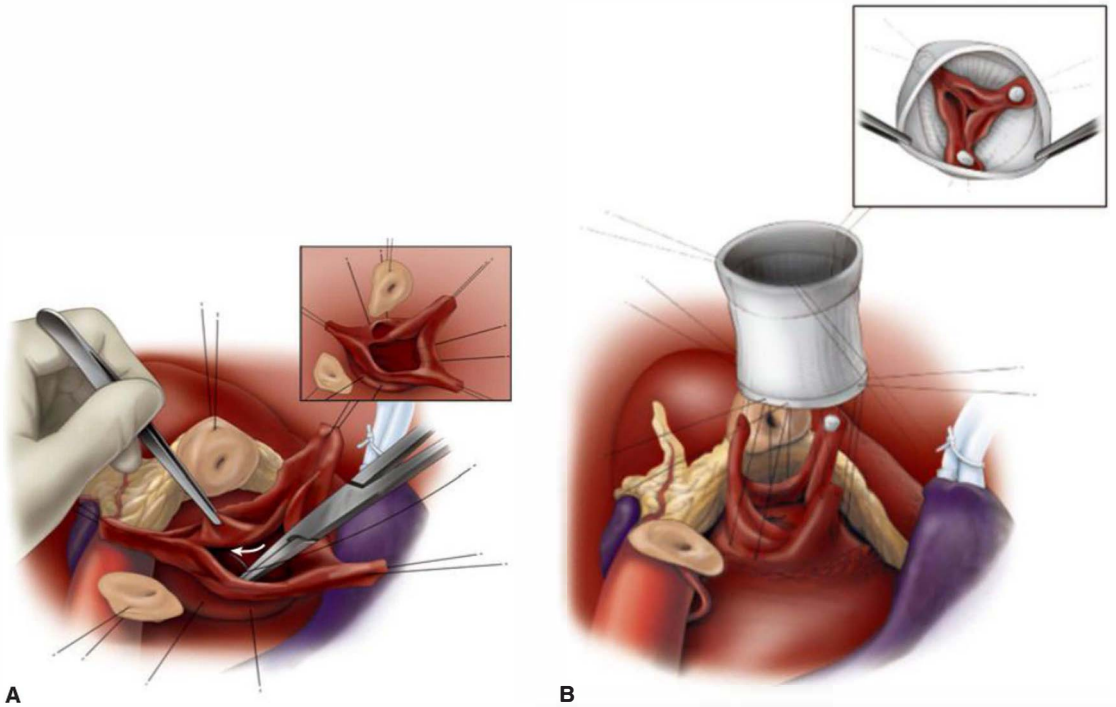



**FIGURE 82-3** **A.** Aortic valve-sparing root replacement (AVSRR). The aortic root is prepared by excision of all three sinuses of Valsalva, leaving 4 to 5 mm of sinus tissue for reimplantation. The coronary arteries are fully mobilized and three mattress sutures are placed below the nadir of the sinuses. (Courtesy of Dr. Duke Cameron, The Johns Hopkins University.) **B.** Johns Hopkins technique for AVSRR: The graft is anchored to a level below the nadir of the aortic annulus by three pledgetted braided sutures, while the commissures are resuspended within the Dacron prosthesis at three equidistant points. The remnants of the sinuses of Valsalva are reimplanted within the prosthesis with running monofilament sutures. (Courtesy of Dr. Duke Cameron, The Johns Hopkins University.)

allows for satisfactory leaflet apposition is found. The size of the graft is then upsized by 2 to 4 mm, to account for the thickness of the aortic wall.

To follow, stay sutures are placed above the takeoff of the coronary arteries, the sinuses are excised and trimmed 4 to 5 mm from the annulus, and the coronary arteries are dissected free from the surrounding tissue.

Single, pledgeted 2-0 Tevdek horizontal stay sutures are placed below the nadir of the annulus in each sinus to anchor the tubular graft at a subannular level.

The commisures are then secured to the sinotubular junction of the graft with pledgeted 5-0 Prolene sutures (Fig. 82-3B). At this point, appropriate positioning of the valve inside the new root is verified and a hemostatic suture between the graft and the aortic wall remnant at the aortic annulus is performed with a running 5-0 Prolene.

The coronary arteries are then reimplanted and their suture lines are reinforced with Teflon felt strips to enhance hemostasis and avert the development of pseudoaneurysms.

The aortic valve is then saline-tested and, if competent, repair is completed by performing the distal aortic suture line, which should be carried out as distal as possible. Replacement of the aortic arch should only be performed in case of dilatation or dissection, and not prophylactically.

The left ventricle is de-aired and the aortic clamp is released. During rewarming of the ventricles, function of the aortic valve is assessed by transesophageal echocardiography. The acceptable amount of residual regurgitation depends on the mechanism. Mild central aortic regurgitation secondary to thickened nodules of Arantius is usually not a cause of progressive aortic valve insufficiency and therefore acceptable. However, any instance of aortic insufficiency greater than mild is considered unacceptable, as is the presence of substantial prolapse. In these cases, the valvular apparatus is likely unstable and its function is bound to eventually deteriorate. Leaflet prolapse (often brought about by graft undersizing) should therefore be promptly addressed.

At the end of the intervention, patients with pectus excavatum may undergo concomitant repair with a Nuss procedure.

## SURGICAL OUTCOMES

Because of earlier diagnosis, an increasing number of patients with syndromic aortic root aneurysms are undergoing surgery during childhood. However, prophylactic aortic root replacement in pediatric patients is still a relatively

novel concept, as both the size of patient population and the length of cumulative follow-up are limited. In addition, identification of new clinical syndromes and the introduction of recent surgical techniques further fragments the study population in multiple, small cohorts. These features account for the little knowledge on treatment outcomes in children with congenital aortopathies.

In absence of long-term data on event-free survival following AVSRR surgery, the Bentall procedure remains as the gold standard for aortic root replacement.[40,41] However, aortic valve preservation offers intuitive advantages over valve replacement, making patients virtually free from infective endocarditis and lifelong anticoagulation. Therefore, and particularly in pediatric patients and young adults, there is widespread interest in performing valve-sparing operations even though long-term durability of such procedures has yet to be ascertained. In particular, aortic valve reimplantation techniques are now the default approach whenever the root anatomy is permissive. As for adults, remodeling techniques should now be considered obsolete in the pediatric population since late aortic root instability and clinically significant aortic valve insufficiency have been reported.[42]

Marfan syndrome is considered the prototype of connective tissue disorders and the one most studied. Yet, only a handful of studies are specifically dedicated to surgical results of children affected by this syndrome, with none of these exclusively focused on aortic root replacement.[40–43] Regardless, these studies demonstrate that aortic root replacement can be accomplished with minimal operative mortality and excellent long-term survival as shown by Kaplan–Meier estimates of 10-year survival that approach 80 percent.[40,41] However, 10-year freedom from operation is as low as 41 percent with the main cause of late reintervention being distal aortic pathology and need for mitral valve repair or replacement.[41] When compared with adults with Marfan syndrome, children have a greater risk of undergoing aortic reoperation; this is intuitive, considering the longer course of the disease and the fact that catastrophic aortic complications are exceedingly rare in children. This, combined with the knowledge that late mortality is primarily attributable to cardiovascular causes, highlights the importance of clinical and radiological surveillance for successful management of these patients, as current prophylactic treatment on the aortic root does not completely eliminate late cardiovascular morbidity.

Early surgical results in patients with Loeys–Dietz syndrome (either type I or type II) are encouraging. In an initial surgical series of 21 patients treated at the Johns Hopkins Hospital, there were no operative deaths or early reoperations. Early aortic valve function was excellent among the valve-sparing group and composite valve graft surgery was reserved for patients deemed not suitable for aortic valve preservation. No hemorrhagic event or infectious endocarditis were observed.[22] However, the main cause of late morbidity and mortality was dissection at sites remote from the previously operated aorta (7 percent of the surgical cohort) due to poor elastic properties of the arteries.[44]

In patients affected by vascular-type Ehlers–Danlos syndrome surgical mortality appears to be greater (10 percent) than in patients with similar connective tissue disorders mostly due to graft-related complications.[25] The most relevant feature of vascular type Ehlers–Danlos syndrome is in fact the extreme fragility of the arterial wall that makes vessels very little tolerant to intraoperative manipulation. Arterial friability is the main reason for the high prevalence of significant postoperative bleeding (46 percent) and late anastomotic complications such as disruption and pseudoaneurysm (40 percent) reported in the literature.[25] Long-term survival after surgery appears nevertheless satisfactory, although below that of the age-matched general population (68 percent at age 50 years).[25] Prevalent causes of late death are associated with anastomotic complications (pseudoaneurysms) and dissection at sites distant from prior vascular surgery. However, to the best of our knowledge no study exclusively dedicated to a pediatric population of Ehlers–Danlos patients has been published at this time.

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## CARDIAC SURGICAL INTERVENTION IN PEDIATRIC PATIENTS WITH CONNECTIVE TISSUE DISORDERS BOARD REVIEW QUESTIONS (CHAPTER 82)

1. Which is correct regarding pathophysiology of connective tissue disorders?
   A. Marfan syndrome is caused by deficiency of fibrillin-2.
   B. Ehlers–Danlos vascular type is associated with alteration of type I collagen.
   C. Bicuspid aortic valve aneurysms are caused by altered elastin production.
   D. Increased TGF-β signaling leads to decreased collagen synthesis.
   E. Molecular events in the adventitia may have a role in aneurysm formation.

2. Which is not a clinical feature of Marfan syndrome?
   A. In 25 percent of patients, the disease presents de novo.
   B. The infantile form is dominated by mitral valve disease.
   C. Rupture of an enlarged root is the leading cause of death in older adolescents.
   D. Aortic regurgitation is common once the root reaches 4 cm in diameter.
   E. Dissection is more common if the root expands at a rate of more than 15 mm/year.

3. Which is not an indication for surgery in patients with connective tissue disorders?
   A. Marfan syndrome and aortic root size 5 cm
   B. Bicuspid aortic valve and aneurysm growth rate 12 mm during the last year
   C. Progressive aortic insufficiency
   D. Family history of premature aortic dissection
   E. Eight-year old patient with *z*-score over 3

4. Which of the following would not be a suitable patient for valve-sparing root replacement?
   A. Acute aortic dissection
   B. Asymmetric valve prolapse
   C. Annulus size 20 mm
   D. Bicuspid aortic valve
   E. Simultaneous mitral valve repair
5. Which of the following is true for outcomes after operative for patients with connective tissue disorders?
   A. Remodeling techniques should be considered obsolete for pediatric patients.
   B. Ten-year survival for root replacement in children with Marfan syndrome is approximately 60 percent.
   C. The main cause for late reintervention in aortic regurgitation
   D. Prophylactic root replacement eliminates late cardiovascular morbidity.
   E. Surgical mortality for patients with Ehlers–Danlos syndrome is similar to other connective tissue disorders.

## ANSWERS

1. **Answer: E.** Recent studies on aneurysm progression emphasize molecular events in the adventitia. Marfan syndrome is caused by deficiency of fibrillin-1. Ehlers–Danlos vascular type is associated with alteration of type III collagen. Bicuspid aortic valve aneurysms are caused by altered collagen production. Increased TGF-β signaling has been observed in various forms of aneurysms and leads to increased collagen synthesis, loss of elastin content, and elastic fiber disarray.
2. **Answer: D.** Aortic regurgitation is rare if the root is less than 6 cm in diameter. The disease presents de novo in 25 percent of individuals. The infantile form is clinically aggressive and is dominated by mitral valve disease. The leading cause of death in older adolescents is aortic root rupture. Dissection is more common if the root expands at a rate exceeding 15 mm/year.
3. **Answer: E.** Z-score is not utilized for young patients with aortic dilation. Accepted indications for surgery include aortic root size of 5 cm, growth rate over 1 cm/year, progressive aortic regurgitation, and family history of premature dissection.
4. **Answer: B.** A grossly abnormal valve with asymmetric leaflet prolapse is generally not suitable for a valve-sparing procedure. Valve-sparing root replacement can be safely and effectively performed in acute dissection and bicuspid aortic valve if the leaflets are normal and competent. Annulus size greater than 18 mm and simultaneous mitral valve repair are also suitable patients.
5. **Answer: A.** Reimplantation techniques are superior to remodeling techniques in children. Ten-year survival for root replacement in children with Marfan syndrome is approximately 80 percent. The main causes for late reintervention are distal aortic pathology and mitral valve disease. Prophylactic root replacement does not completely eliminate late cardiovascular morbidity. Surgical mortality for patients with Ehlers–Danlos syndrome is greater than other forms of connective tissue disorders.

83

# Surgery for Congenital Coronary Artery Anomalies

*Julie A. Brothers*
*J. William Gaynor*

## INTRODUCTION

This chapter focuses on the management of coronary artery anomalies in patients without other hemodynamically significant heart defects. Although most coronary artery anomalies are of intellectual interest only, there are a few that are clinically significant as they may result in myocardial ischemia, left ventricular dysfunction, and sudden death. The clinically significant anomalies that we will discuss in this chapter are: anomalous origin of a coronary artery from the pulmonary artery, anomalous coronary artery that courses between the aorta and the pulmonary artery, and coronary artery fistulae.

Normally, two coronary arteries arise from separate ostia in the right and left aortic sinuses of Valsalva. The left main coronary artery (LMCA) originates from the left sinus and usually bifurcates into the left anterior descending (LAD) coronary artery and left circumflex coronary artery. The LAD courses in the anterior interventricular groove while the left circumflex coronary artery runs in the left atrioventricular groove. The right coronary artery (RCA) originates anteriorly from the right aortic sinus, runs along the right atrioventricular groove, and usually terminates as the posterior descending artery.

The coronary artery ostia are usually centrally located in the appropriate sinus of Valsalva. However, the ostium may be eccentrically located in some individuals, with the ostium arising close to a valve commissure. The coronary ostia may have a "high takeoff" from the tubular aorta above the sinotubular junction, which is usually benign. It is important to be aware of this anomaly if one needs an aortic valve replacement or requires an aortotomy for another reason, as the coronary artery can be transected if not recognized prior to surgery. When both coronary arteries arise from the same aortic sinus with either a single ostium or two separate ostia (Table 83-1), the anomaly is usually benign if the anomalous vessel courses posterior to the aorta or anterior to the pulmonary artery. However, if either the anomalous LMCA or RCA courses between the two great vessels, this may lead to myocardial ischemia and sudden death.

## ANOMALOUS ORIGIN OF A CORONARY ARTERY FROM THE PULMONARY ARTERY

Anomalous origin of a coronary artery from the pulmonary artery is a rare congenital coronary anomaly that almost always results in early death if not diagnosed and treated promptly.[1,2] Anomalous origin of the LMCA from the pulmonary artery (ALCAPA) is the most common of this class of coronary anomalies and is associated with myocardial ischemia and left ventricular dysfunction. Much less frequently, the RCA may arise from the pulmonary artery in isolation. In extremely rare and usually fatal circumstances, the LAD, the circumflex, or both the LMCA and RCA may arise aberrantly from the pulmonary artery.

ALCAPA is otherwise known as the Bland-White-Garland syndrome after Bland and colleagues reported in 1933 on the clinical and autopsy findings of an infant with this anomaly.[3] The incidence of ALCAPA ranges from 1 in 30,000 to 1 in 300,000 individuals. In childhood, this anomaly is the most common cause of myocardial infarction and, if not treated, is associated with a 90 percent mortality rate by age 1 year.

### Anatomy

In ALCAPA, the LMCA generally arises from the main pulmonary artery (MPA), although it may arise from the right pulmonary artery. The LMCA most often originates from the rightward aspect of the posterior (facing) sinus of the

**TABLE 83-1: Origin of Both Coronary Arteries from One Sinus**

1. Left main coronary artery originates from right sinus of Valsalva (either from right coronary artery or separate ostia).
   - Left main coronary artery courses anterior to pulmonary artery.
   - Left main coronary artery courses through interventricular septum.
   - Left main coronary artery courses between aorta and pulmonary artery.
   - Left main coronary artery courses posterior to aorta.
   - Rarely the left anterior descending coronary or left circumflex coronary artery alone may originate from the right sinus.
2. Single left main coronary artery arises from the left sinus and bifurcates into the left anterior descending coronary and left circumflex coronary arteries. The left circumflex coronary artery crosses the crux and continues as the right coronary artery.
3. Single right coronary artery from right sinus, which crosses crux, continues as left anterior descending coronary artery and left circumflex coronary artery.
4. Right coronary artery originates from left sinus of Valsalva (either from left main coronary artery or as separate ostium).
   - Right coronary artery courses posterior to aorta.
   - Right coronary artery courses anterior to pulmonary artery.
   - Right coronary artery courses between aorta and pulmonary artery.

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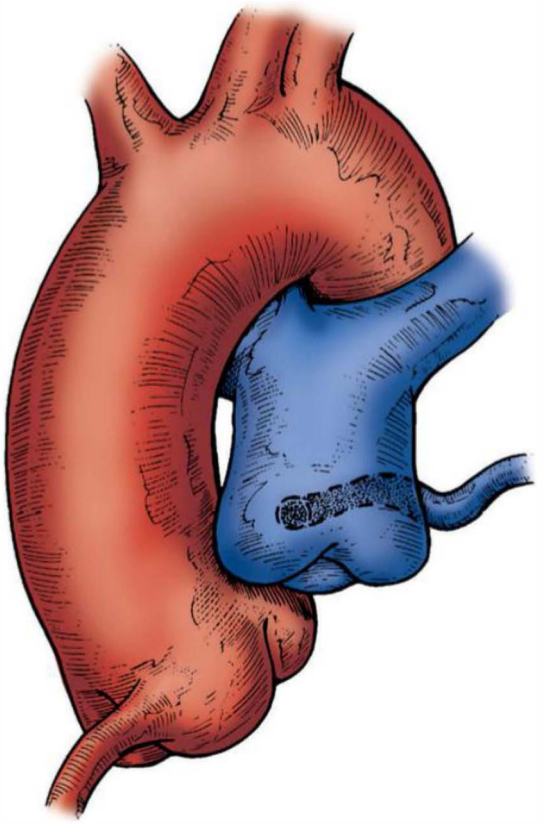


**FIGURE 83-1** The aorta and pulmonary artery showing anomalous origin of the left main coronary artery from the posterior facing sinus of the pulmonary artery with the anomalous artery coursing behind the pulmonary artery. (Reprinted with permission from Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

MPA (Figs. 83-1 and 83-2A–C). Other locations it may originate from are the leftward aspect of the posterior (facing) sinus and, rarely, the anterior (nonfacing) sinus of the MPA (Fig. 83-2C). In the case of an anomalous RCA, the most common location is originating from the anterior portion of the pulmonary artery.

Other associated defects with ALCAPA may include patent ductus arteriosus (PDA), ventricular septal defect (VSD), coarctation of the aorta, and tetralogy of Fallot.

## Pathophysiology

During fetal life, the systemic and pulmonary circulation pressures are similar; therefore, in children with ALCAPA, myocardial perfusion remains intact since the pulmonary arterial pressure is systemic. After birth but before ductal closure, the pulmonary artery pressure remains elevated, thus allowing adequate perfusion of the anomalous coronary artery. Because of this, diagnosis of ALCAPA in the first few days of life is rare. Children with ALCAPA will usually develop symptoms after ductal closure and the subsequent fall in the pulmonary vascular resistance. However, the clinical course after ductal closure varies and is largely dependent on the presence or absence of collaterals from the RCA to the left coronary system. If the collateral circulation has not been well established, myocardial ischemia and ventricular dysfunction rapidly occur due to inadequate myocardial perfusion.[4] Because the pulmonary artery pressure is lower than the systemic pressure, the left ventricle is being perfused with desaturated blood. If there is a PDA or VSD, the pulmonary artery pressure may be elevated, so that the left ventricular perfusion pressure may be adequate and ischemia may not occur. If ALCAPA is not diagnosed prior to closure of these defects, it will become apparent shortly thereafter when the pulmonary arterial pressure drops; the outcome is usually fatal.

If adequate collateralization has been established, then perfusion of the left coronary system is maintained. However, as the pulmonary vascular resistance falls, a shunt develops from the RCA to the pulmonary artery. The RCA and left coronary artery systems progressively dilate with flow reversal in the left coronary leading to a pulmonary-coronary steal. Although the overall shunt is relatively small related to cardiac output, it is significant with regards to coronary blood flow. Children with an extensive collateral system may survive past infancy; however, progressive left

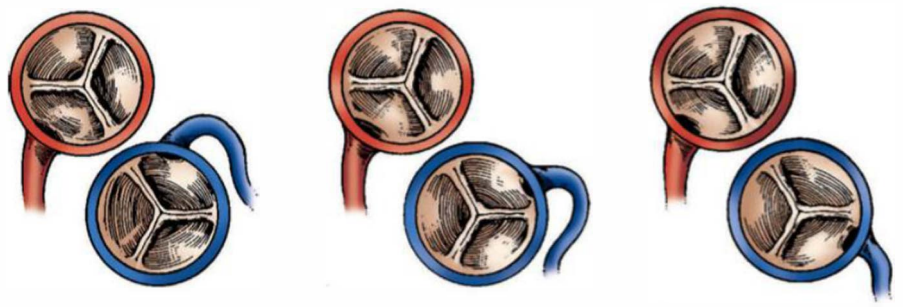



**FIGURE 83-2** **A.** Anomalous origin of left main coronary artery from the rightward aspect of the posterior facing sinus of the pulmonary artery. **B.** Anomalous origin of the left main coronary artery from the leftward aspect of the posterior facing sinus. **C.** Anomalous origin of the left main coronary artery from the nonfacing sinus of the pulmonary artery. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

ventricular dysfunction will predictably ensue.[5] In a small number of patients, the collateral vessels are enough to maintain adequate myocardial perfusion at rest and sometimes even during exertion. Because of this, these patients may not be diagnosed until adulthood.[6] This is rare, however, and most children have severe mitral regurgitation (MR) due to infarction of the posterior leaflet of the mitral valve and subsequent poor movement of the leaflet as well as ventricular dilation; fibrosis and fibroelastosis of the papillary muscle may also be present.

## Clinical Presentation

Clinical presentation is usually between 4 and 6 weeks of age when the pulmonary vascular resistance has dropped[7]; however, sometimes infants are not diagnosed until 2 to 3 months of age when symptoms have increased in severity. Presenting signs and symptoms are those of congestive heart failure, including sweating and discomfort with feeding, tachypnea, poor weight gain, and pallor. The apparent discomfort with feeding is thought to represent myocardial ischemia. Those not identified as infants are usually diagnosed at several months of age due to a loud MR murmur. Those not diagnosed during infancy may remain asymptomatic, while others may present with exertional chest pain, presyncope, or syncope. Furthermore, there have been reports of exertional sudden death in older patients. Patients with anomalous origin of the RCA from the pulmonary artery tend to have symptoms to ALCAPA but they may be less severe; however, myocardial ischemia and sudden death can still occur.

On physical examination, an infant with ALCAPA may demonstrate signs of congestive heart failure, including tachypnea, tachycardia, and hepatomegaly. Distinguishing left ventricular dysfunction secondary to ALCAPA from dilated cardiomyopathy can be difficult. Cardiac examination may demonstrate a gallop rhythm and a systolic murmur of MR at the apex. If pulmonary hypertension is present due to left ventricular failure, there may be evidence of right heart enlargement and an accentuated pulmonary component of the second heart sound on examination.

Chest radiography in infants with ALCAPA generally demonstrates an enlarged cardiac silhouette, mainly due to the enlarged left atrium and left ventricle. In those with congestive heart failure, electrocardiogram (ECG) can be a useful diagnostic clue. Classically, there is evidence of lateral or anterolateral wall infarction with Q waves and ST segment elevation in leads I, aVL, and V4-V6. While these electrocardiographic abnormalities can be found in other causes of myocardial infarction or cardiomyopathy, if they are seen in an infant in congestive heart failure, the diagnosis of ALCAPA needs to be strongly considered. Indeed, any infant with dilated cardiomyopathy must be extensively evaluated to rule out ALCAPA. This diagnosis must also be entertained in older children and adolescents with dilated cardiomyopathy since there are patients who survive past infancy.

## Diagnostic Imaging

Echocardiography with Doppler color flow usually shows a dilated left ventricle with some degree of MR. An enlarged RCA is almost always noted and should increase suspicion of this diagnosis. Visualization of the origin of both coronary arteries is necessary with the objective of demonstrating the origin of the LMCA from the pulmonary artery. If visualization of the anomalous vessel is difficult, color flow Doppler may be used to show retrograde flow from the LMCA into the pulmonary artery. Nevertheless, if any questions remain about location of both coronary ostia, then cardiac catheterization is mandatory to rule out ALCAPA.

Cardiac catheterization with angiography is the gold standard in diagnosing ALCAPA. In infants with ALCAPA, hemodynamic data may demonstrate elevated filling and pulmonary arterial pressures and a low cardiac output. In older

asymptomatic patients, hemodynamic data may show only slightly elevated pulmonary arterial pressures with normal filling pressures and a normal cardiac output. Catheterization data may show a small left-to-right shunt. On aortic root injection, a single, dilated RCA will arise normally from the aorta. If there are significant collaterals, aortic root angiography will demonstrate the collateral blood flow providing late, retrograde filling of the LMCA and a blush of contrast subsequently filling the MPA. Furthermore, if there are significant collaterals with a resultant large left–right shunt, a step-up in oxygen saturation may be noted in the MPA. If the diagnosis remains in doubt, a distal balloon occlusion of the MPA with proximal injection should demonstrate the anomalous LCA.[8]

Magnetic resonance imaging (MRI) has emerged as a useful noninvasive diagnostic tool for delineating congenital coronary anomalies.[9,10] Studies have shown that magnetic resonance angiography has a similar sensitivity and specificity compared to coronary angiography and may be particularly useful in delineating the proximal course of anomalous coronary arteries. Further data are needed before recommending MRI instead of cardiac catheterization. In adults, computed tomography (CT) scan has been used extensively for coronary artery delineation. Although CT scan may be useful in the older patients diagnosed with ALCAPA, exposure to radiation and the need for a slower heart rate with ECG gating generally excludes its use in infants.

## Surgical Management

### INDICATIONS

Surgical repair is necessary in all patients with ALCAPA. Even in infants who present in congestive heart failure, surgery should occur shortly following diagnosis, as the risk of further myocardial ischemia and subsequent death is high.[11] In older asymptomatic patients, surgery can be performed electively. If an infant presents in significant heart failure, surgery will likely need to be delayed for at least 24 hours to stabilize the patient using mechanical ventilation, inotropic support, and vasodilators, when necessary. As reported by Del Nido and colleagues, even the sickest infants can withstand surgical repair if left ventricular assist devices (LVAD) are utilized postoperatively.[12] Other critically ill infants may need extracorporeal membrane oxygenation (ECMO). It is important that centers performing ALCAPA surgery have the capability to provide mechanical assistance if necessary; if not, the child should be transferred to a hospital where these services are available.

Restoring a two-coronary system is the surgical goal. Simple ligation of the anomalous coronary should not be performed.[13] Furthermore, because significant recovery of heart function usually occurs postoperatively, infants presenting with severe left ventricular dysfunction and mitral insufficiency should not be excluded from revascularization. Even if severe MR is present at diagnosis, left ventricular aneurysmectomy and mitral valve repair or replacement are rarely indicated at the time of initial procedure because the severity of MR almost always diminishes after revascularization.

### SURGICAL TECHNIQUES

The first successful operation for ALCAPA consisted of ligation of the anomalous vessel at the pulmonary artery, thus preventing the left-to-right shunt. This procedure allowed perfusion of the left ventricle through collaterals from the RCA. However, there was significant operative mortality and risk of late sudden death with this procedure, so a variety of alternative techniques were developed to create a dual coronary artery system. These included coronary artery bypass grafting, creation of an aortopulmonary window, and direct coronary reimplantation.

Coronary artery bypass grafts utilized the left subclavian artery, the internal mammary artery (IMA), and saphenous vein. The first successful left subclavian artery-to-left coronary bypass was first reported in 1968[14]; however, the results of bypass grafting, notably with saphenous vein grafts, have been disappointing. The creation of an aortopulmonary window and intrapulmonary artery baffle using a pulmonary artery flap to direct blood flow from the aorta to the anomalous coronary artery was first described by Takeuchi and associates.[15] As experience with the arterial switch operation for transposition of the great vessels has increased, the procedure of choice currently utilized in most institutions is direct reimplantation of the anomalous coronary into the aorta.[16,17]

***Coronary Artery Bypass Grafting.*** Coronary artery bypass grafting is rarely utilized in patients with ALCAPA. If necessary, it is typically used as a way to create a dual coronary artery system after previous ligation or due to stenosis or occlusion after a previous attempt at repair. In these cases, the IMA is the conduit of choice and can be successfully used even in neonates and infants. There is some evidence for growth of the IMA after bypass grafting[18–20] in pediatric patients. Grafts using the saphenous vein are not recommended due to the risk of occlusion and poor long-term results,[21] and should only be utilized if no other option is available. Similarly, left subclavian-to-left coronary artery anastomosis is not frequently utilized due to the risk of stenosis or occlusion.[22,23]

***Direct Reimplantation.*** Direct reimplantation of the anomalous coronary artery onto the aorta can be performed in most patients with ALCAPA (Figs. 83-3–83-6).[24,25] The procedure is fairly straightforward when the anomalous coronary ostium is in the posterior-facing sinus. Even if the ostium is located in the non-facing sinus, direct implantation is possible by excising a large button of pulmonary artery to extend the coronary artery.

A median sternotomy is performed after induction of anesthesia and placement of monitoring lines. The thymus is resected. The pericardium is opened and suspended in stay sutures. Contact with the myocardium should be kept at a minimum until the patient is placed on cardiopulmonary bypass due to the risk of ventricular fibrillation from

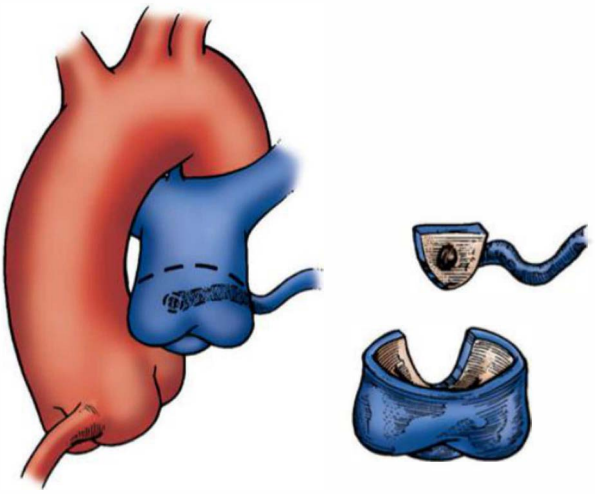


**FIGURE 83-3** After institution of cardiopulmonary bypass and induction of cardioplegia, the pulmonary artery is transected above the sinotubular junction and the anomalous coronary ostium excised with a generous button of pulmonary artery wall. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

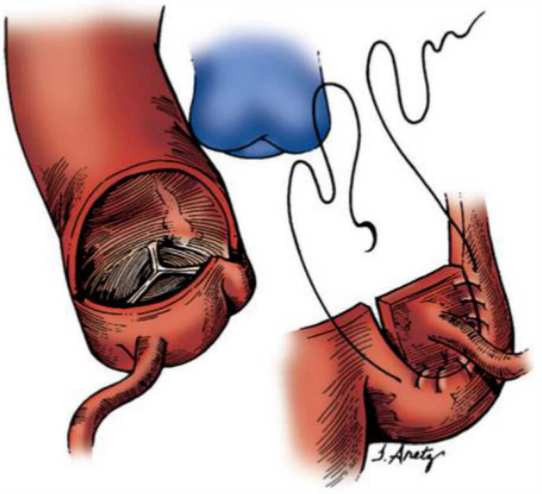


**FIGURE 83-5** After the anomalous coronary artery is mobilized, the aorta is opened transversely above the sinotubular junction and a vertical incision is made in the left posterior sinus to accept the reimplanted coronary. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

myocardial ischemia and left ventricular dysfunction. This operation may be performed using either continuous low-flow bypass with moderate hypothermia (25–28°C) or deep hypothermic circulatory arrest (18°C) in very small infants. An aortic purse-string suture is placed distally near the innominate artery and another is placed in the right atrial appendage for a single venous cannula prior to cannulation. Heparin is administered, the aortic and right atrial cannulae are inserted, and cardiopulmonary bypass is established. Decompression of the left ventricle should be performed by placing a left ventricular vent via the right superior pulmonary vein. Although on bypass, the pulmonary artery and

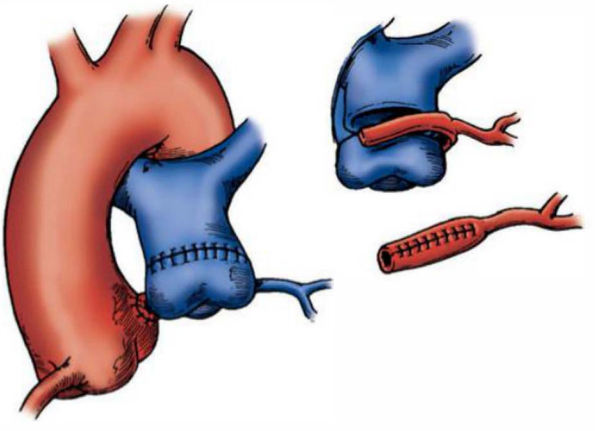


**FIGURE 83-4** Occasionally when the coronary artery arises from the leftward or anterior aspect of the pulmonary artery, direct reimplantation may not be possible. In these situations, a tube can be constructed from a segment of pulmonary artery to lengthen the coronary and allow reimplantation on the aorta. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

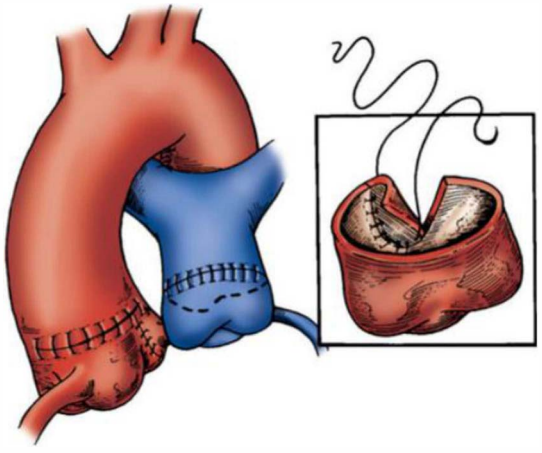


**FIGURE 83-6** After the coronary is reimplanted, the aorta is closed primarily. The pulmonary artery may frequently be closed primarily. Ligation and division of the ligamentum arteriosus improves mobility of pulmonary artery. Occasionally, patch repair of the defect in the pulmonary artery with autologous pericardium may be necessary (inset). (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

epicardial course of the left coronary artery are visualized. Direct reimplantation may not be possible if the anomalous left coronary originates far leftward in the posterior-facing sinus or on the anterior non-facing sinus.

The aorta and both pulmonary arteries are fully mobilized. The ductus (or ligamentum) arteriosus is ligated to improve mobility of the pulmonary artery. Tourniquets are placed around both the right and left branch pulmonary arteries to occlude the branch pulmonary arteries and prevent run-off of cardioplegia solution into the lungs. Another way to prevent run-off is to compress the coronary artery origin from the pulmonary artery during administration of cardioplegia solution. A cannula is inserted in the ascending aorta for administration of cardioplegia solution, the aorta is cross-clamped, and cold cardioplegia is administered via the aortic root. If circulatory arrest is utilized, the head vessels are then occluded with tourniquets, the circulation is arrested, venous blood is drained into the reservoir, and the cannulae are removed.

After adequate arrest, the pulmonary artery is opened transversely just above the sinotubular junction (Fig. 83-3) and the anomalous coronary orifice is noted. Similar to the procedure used for the arterial switch operation, the pulmonary artery is divided and the coronary ostium is excised from the posterior aspect of the pulmonary artery using a generous button of arterial wall. The excised segment of the pulmonary wall extends the proximal end of the coronary artery, thereby allowing for the aortic anastomosis to be accomplished without tension. The pulmonary commissure may need to be taken down if the coronary ostium is located near a commissure. Alternatively, if the coronary arises anteriorly from the pulmonary artery or from a branch pulmonary artery and above the commissures, one can extend the coronary artery by using a tube constructed from pulmonary artery wall to allow reimplantation (Fig. 83-4). The proximal portion of the coronary artery is mobilized using cautery, exercising caution to avoid any small branches. Just as in the arterial switch operation, the aorta is then opened transversely directly above the sinotubular junction and the incision is carried posteriorly over the left posterior-facing sinus (Fig. 83-5). The sinus is then incised vertically to accept the coronary button. The coronary button is carefully aligned with the aortic incision to avoid twisting or kinking. Using a continuous suture of 7-0 polypropylene (Prolene), the anastomosis is begun at the most inferior aspect of the coronary button, which is attached to the most inferior aspect of the incision in the sinus. The suture line is carried to the top of the incision anteriorly and posteriorly. The aorta is closed using a continuous suture of 7-0 Prolene, which is tied to the coronary button suture as the anastomosis is completed (Fig. 83-5). After aortic closure, cardioplegia solution is administered and the anastomotic site is inspected for adequate filling of the coronary as well as for hemostasis.

In most cases, the pulmonary artery can be repaired using a continuous suture of 7-0 Prolene. Division of the ductus will improve mobility of the pulmonary artery confluence and allow reconstruction without tension. If there is tension or narrowing, or if the defect left by excision of the coronary artery button is sizeable, the pulmonary artery should be repaired with a patch of autologous pericardium (Fig. 83-6). If a commissure was taken down during excision of the coronary button, the pulmonary artery should be reconstructed with pericardium and the commissure resuspended.

The patient is then rewarmed and the aortic cross-clamp is removed. Alternatively, the cross-clamp may be removed before the pulmonary artery reconstruction to minimize ischemic time. The left ventricle is inspected to assess for adequacy of perfusion, and suture lines are inspected for hemostasis. Right and left atrial lines are placed to adequately monitor pressure and for drug administration. Atrial and ventricular pacing wires are also placed. The patient is separated from cardiopulmonary bypass after complete rewarming.

The ECG should be monitored closely for evidence of ischemia during reperfusion and after separation from bypass. Inotropic support may be temporarily necessary due to preoperative left ventricular dysfunction.

***Modified Takeuchi Operation.*** The Takeuchi operation, or intrapulmonary artery tunnel, is an alternative surgical strategy for repair of ALCAPA. Takeuchi and colleagues first described the creation of an aortopulmonary window using a portion of the anterior pulmonary artery wall to create a baffle which would direct blood from the aorta to the anomalously located left coronary artery ostium.[15] In the modified repair, a polytetrafluoroethylene (PTFE, Gore-Tex) patch is used to construct the baffle. However, creating a baffle may not be possible if the ostium is located near a commissure or arises from a branch pulmonary artery.

The procedure may be performed with either continuous low-flow cardiopulmonary bypass (25–28°C) or deep hypothermic circulatory arrest (18°C). Cannulation is performed as described above for direct reimplantation. After induction of cardioplegic arrest, a longitudinal incision is made in the anterior portion of the pulmonary artery (Fig. 83-7) and the ostium of the anomalous coronary is identified. Using a punch, a 5-mm diameter opening is made on the leftward aspect of the aorta above the sinotubular junction (Fig. 83-8). If there is any question regarding placement of the aortic opening, an anterior aortotomy should be performed and the incision visualized directly to avoid damage to the aortic valve. By creating the aortopulmonary window above the sinotubular junction, this allows a downward angle of the baffle into the sinus if the ostium is located deep within a sinus. After a similar incision is made in the pulmonary artery directly opposite to the aortic opening, these are anastomosed using a continuous suture of 7-0 Prolene creating an aortopulmonary window (Fig. 83-8). A 4-mm PTFE tube graft is split longitudinally and customized to an appropriate length (Fig. 83-9). This graft functions as an intrapulmonary artery tunnel, baffling blood from the aortopulmonary window to the anomalous coronary ostium. The suture line starts at the anomalous coronary and is continued inferiorly along the pulmonary artery wall to the aortopulmonary window. The suture line then returns to the coronary artery to complete the superior aspect of the baffle.

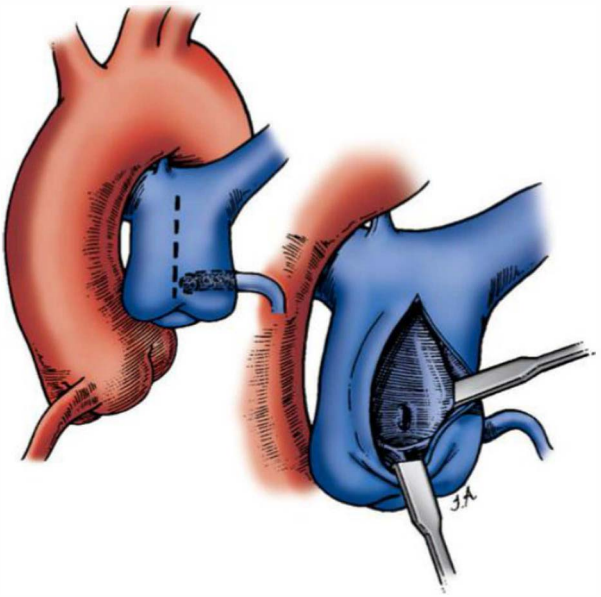


**FIGURE 83-7** After institution of cardiopulmonary bypass and induction of cardioplegia, a longitudinal incision is made in the main pulmonary artery, and the ostium of the abnormal coronary is identified. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

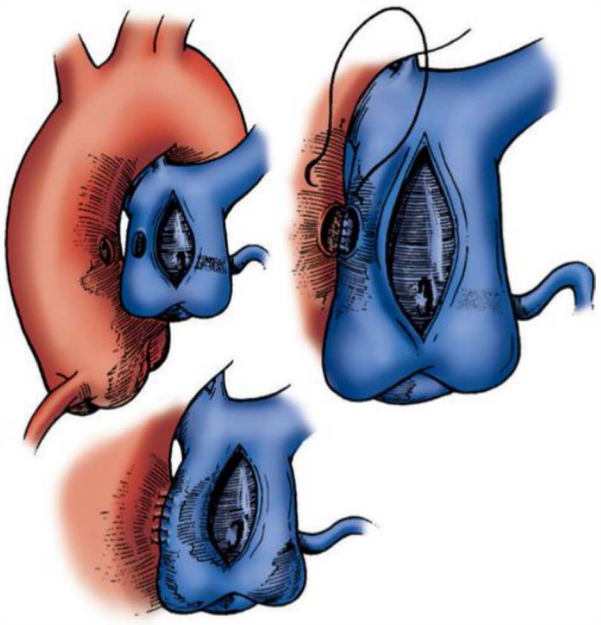


**FIGURE 83-8** Using a punch, a 5-mm opening is made in the aorta on the leftward aspect above the sinotubular junction. A similar opening is made in the pulmonary artery at the same level, and these are anastomosed to create an aortopulmonary window. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

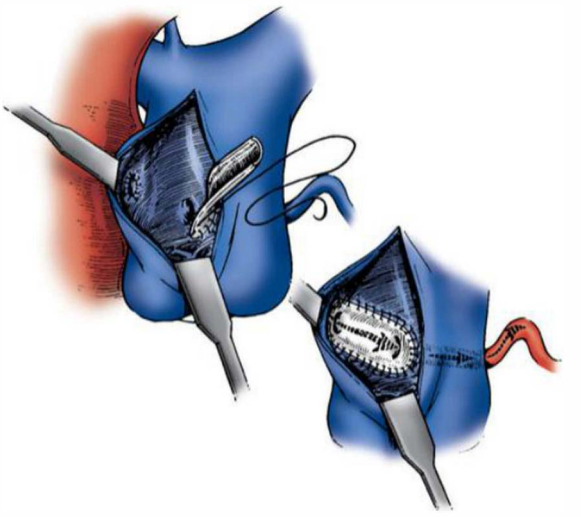


**FIGURE 83-9** A segment of 4-mm polytetrafluoroethylene (Gore-Tex) graft is opened longitudinally and used to fashion a baffle that directs blood flow from the aortopulmonary window to the anomalous coronary ostium. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

After the baffle is created, repair of the pulmonary artery is performed using a prosthetic patch or autologous pericardium to avoid supravalvar pulmonary artery obstruction (Fig. 83-10). The most common complications of the modified Takeuchi operation include baffle leak, baffle occlusion, and supravalvar pulmonary artery obstruction.

## Postoperative Management

Regardless of which surgical technique was utilized, the most common postoperative issues are those related to the infant's preoperative state: low cardiac output, left ventricular dysfunction, and hypotension. Optimizing the patient's hemoglobin, electrolytes, acid-base and fluid status, and providing adequate inotropic support are extremely important. LVAD or ECMO support may be temporarily necessary in infants and children with severe preoperative cardiac dysfunction. Bleeding is also a common postoperative issue and is more frequently encountered in small infants and those who require mechanical support. Platelets and fresh frozen plasma should be used aggressively to replace ongoing losses. Patients with low cardiac output and/or bleeding issues may be candidates for delayed sternal closure.

## Results

Although simple ligation of ALCAPA has unacceptable early and late mortality rates, survival after establishment of a dual coronary system is generally excellent.[13,26] Bunton and

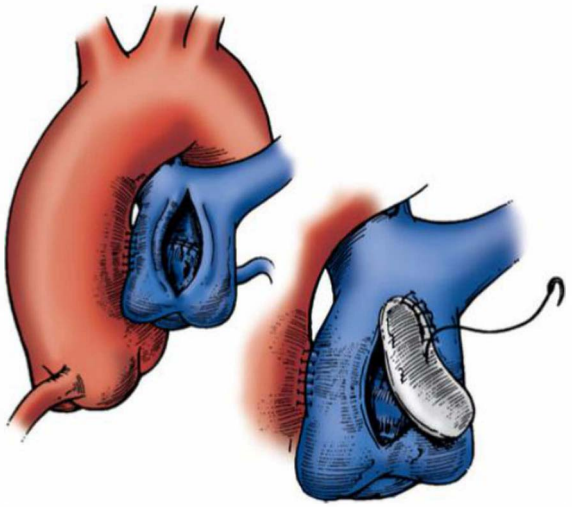


**FIGURE 83-10** After the baffle is completed, the pulmonary arteriotomy is repaired with a patch to avoid creation of supravalvar right ventricular outflow tract obstruction. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

colleagues reported in 1987 on 24 patients with ALCAPA: 11 had coronary ligation or ostial closure, 11 underwent a Takeuchi repair, and 2 had other procedures.[27] Over an average 10.5-year follow-up period, those who underwent coronary ligation or ostial closure had a 27 percent early mortality and a 25 percent late mortality rate. On the other hand, there were no early or late deaths over an 18.5-month follow-up period in those who underwent the Takeuchi procedure. After Takeuchi repair, two patients developed right ventricular outflow tract obstruction and one patient had baffle occlusion. Backer and colleagues reported the follow-up surgical results of 20 patients with ALCAPA who underwent different procedures.[28] There were two early deaths and one late death out of nine patients who underwent ligation, but there were no deaths among the 10 patients who underwent creation of a dual coronary artery system or the 1 patient who had cardiac transplantation. Of five patients who had left subclavian-to-left coronary anastomosis, two developed significant anastomotic stenosis. Vouhe and associates from Paris reported on coronary reimplantation in 31 consecutive children.[29] Within the first 3 months, there were three hospital deaths and two additional deaths, but no late deaths. The only risk factor identified for early mortality was poor cardiac function. The survivors were studied for more than 1 year after repair and all had normal left ventricular function. In five of seven patients who had severe MR preoperatively, the severity had decreased to mild or no regurgitation. The reimplanted coronary artery was patent in all patients. Lange and colleagues recently reviewed the long-term results of 56 patients with ALCAPA who underwent either subclavian artery anastomosis or coronary artery transfer.[30] Patients who had a Takeuchi procedure or a left IMA graft were excluded. Both surgical groups had similar early mortality rates of 14 percent but no mortality in those undergoing repair in the last 13 years. There was one late death in each surgical group. At final follow-up (mean 14.5 years for subclavian artery group and 8.7 years for coronary transfer group), 95 percent of patients had normal left ventricular function and 84 percent had only mild MR. Although the prospect of functional recovery is excellent, cardiac transplantation may be indicated if left ventricular function does not improve following the revascularization procedure.

## Special Considerations

### MITRAL REGURGITATION

The management of MR during the initial surgery is controversial.[31] In general, at least a moderate degree of MR is present initially in most patients. Even in patients with severe MR, there are several reports of significant improvement after coronary reperfusion alone. This is likely due to improved left ventricular function and a decrease in left ventricular size postoperatively. Valve repair at the time of initial surgery can result in longer ischemic times and can be technically more difficult to perform in an infant heart compared to an older child. However, some advocate routine annuloplasty at the time of initial repair whereas others recommend annuloplasty or mitral valve replacement only with severe MR.[32] In summary, early surgical repair of the mitral valve is generally not necessary. If valve repair due to severe MR is needed later, it is likely to be more successful and easier to do technically. If severe MR persists late postoperatively, possible causes of ongoing myocardial ischemia should be investigated.

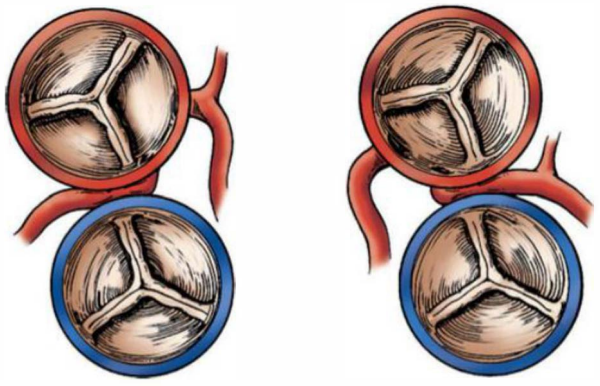
### LATE PRESENTATION IN THE ADULT

As discussed previously, adults who present with ALCAPA are rare but do occur. Surgery is indicated in all cases but can generally be done electively. In adults, the surgical choice is coronary bypass grafting using the left internal thoracic artery in association with ligation of the proximal vessel; this is generally a low-risk procedure that all adult cardiothoracic surgeons can perform with a low mortality rate.

# ANOMALOUS CORONARY ARTERY COURSE BETWEEN AORTA AND PULMONARY ARTERY

## Anatomy

An anomalous coronary artery that courses between the two great vessels is associated with an increased risk of myocardial ischemia and sudden death, notably in children and young adults. When there are two separate ostia in the same



A B

**FIGURE 83-11** **A.** Anomalous origin of the right coronary artery from the left aortic sinus with abnormal coursing of the right coronary artery between the aorta and pulmonary artery. **B.** Abnormal origin of the left main coronary artery from the right aortic sinus with abnormal coursing of the left main coronary artery between the aorta and pulmonary artery. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds): Mastery of cardiothoracic surgery. Philadelphia: Lippincott-Raven, 2007).

sinus of Valsalva, either the aberrant RCA or LMCA may subsequently run intramurally between the great vessels (Fig. 83-11).[33] When the two ostia arise from the same sinus, the anomalous coronary ostium is usually small and slit-like with an acute-angle takeoff from the aorta.[34] Another potential high-risk situation occurs when a single coronary artery arises from the right aortic sinus and the LMCA or LAD runs intramurally between the aorta and pulmonary artery, or if the single coronary arises from the left aortic sinus and the RCA courses intramurally between the great vessels.[35–38]

## Pathophysiology

When the aberrant vessel courses intramurally in the aortic wall between the two great vessels, this anatomy is associated with increased incidence of sudden death.[39–45] Both anomalous LMCA from the right sinus and RCA from the left sinus are associated with sudden death, but the former carries a higher risk. Based on autopsy studies of anomalous coronary artery patients, sudden cardiac death is thought to occur from decreased anomalous coronary blood flow resulting in myocardial ischemia and/or ventricular tachyarrhythmias. This diminished blood flow is likely due to an anatomical malformation of the anomalous vessel, including the narrow slit-like orifice as well as the systolic lateral compression of the anomalous vessel as it courses intramurally. The greatest risk of ischemia and sudden death is during or just after completing vigorous exercise when myocardial oxygen demand and cardiac output are greatest.[46–48]

## Clinical Presentation

The true prevalence of this anomaly is unknown because there is no denominator; however, estimates range from 0.1 to 0.3 percent of the general population.[49–51] What makes this diagnosis especially challenging is that there are no characteristic physical findings. Indeed, the physical examination is almost always normal. What often prompts the referral to a cardiologist is an innocent heart murmur: A carefully performed echocardiogram will then lead to the diagnosis. Many patients with this anomaly are asymptomatic and the initial presentation is sudden death.[49,52] When symptoms are present, they most commonly include chest pain, palpitations, presyncope or syncope during or just following exertion.[33,42,53–55] This diagnosis must be considered in any young patient with exercise-induced complaints suggestive of myocardial ischemia, or in those presenting with aborted sudden death or sudden death.[56] Screening first-degree relatives using echocardiography has recently been suggested due to the potential familial link with this anomaly.[53]

## Diagnostic Imaging

Anyone presenting with presyncope, syncope or chest pain during or just after exertion requires attention and further clinical evaluation. A resting ECG should be obtained to evaluate for ventricular hypertrophy, arrhythmias, and evidence of previous myocardial infarction.

Transthoracic echocardiography with color Doppler is necessary to document normal intracardiac anatomy and to evaluate heart function, especially focusing on areas of abnormal wall motion as clue of possible ischemia.[53,54,57] Close attention should be paid to the coronary artery origins and proximal coronary anatomy. Improvements in two-dimensional echocardiography have made the identification of both coronary artery origins possible in many patients. However, when using traditional two-dimensional imaging alone, the anomalous vessel may appear to arise normally where it exits the aorta. Color Doppler imaging can be quite useful in demonstrating the direction of blood flow within the aortic wall, thus helping to differentiate an anomalous vessel from one that arises normally.

Other noninvasive techniques, such as MRI or CT scan, may be used when the coronary artery origins cannot be adequately delineated and/or to confirm the diagnosis.[58,59] Occasionally cardiac catheterization with angiography or transesophageal echocardiography will be utilized to visualize the coronary anatomy; however, these are more invasive options and are generally not the first choice in children. Indeed, although cardiac catheterization with coronary angiography still remains the gold standard for detecting anomalous coronary arteries, it is being replaced by noninvasive imaging as described above. Coronary angiography may be necessary in adult patients to delineate associated coronary atherosclerotic disease prior to undergoing surgical intervention.[60]

Most patients who are asymptomatic will undergo further evaluation for myocardial ischemia. This usually includes an

exercise stress test with an imaging study, such as a nuclear perfusion scan or stress echocardiography. However, basing management decisions on a single exercise test is not recommended since ischemia is intermittent with this anomaly. In a study by Brothers and colleagues, of nine children who presented with cardiovascular symptoms and who also had a preoperative exercise test, only one demonstrated an abnormality during maximal exercise testing.[33] Furthermore, sudden death has been extensively reported in patients negative results on previous stress-testing.

## Surgical Management

### INDICATIONS FOR SURGERY

Surgical intervention is indicated in any patient with anomalous coronary artery with an interarterial and intramural course who has signs and/or symptoms of myocardial ischemia or ventricular arrhythmias. Most would also agree that surgery is indicated in asymptomatic patients with anomalous origin and course of the LMCA because of the high risk of sudden death observed in this subgroup of patients. The management of asymptomatic patients with anomalous RCA remains controversial.

### UNROOFING PROCEDURE

The unroofing procedure has become the procedure of choice for patients with anomalous coronary artery with an interarterial and intramural course.[33,54,61,62] After a median sternotomy is performed, the pericardium is opened and the anatomy is inspected. Aortic cannulation occurs near the innominate artery and a two-stage venous cannula is inserted via the right atrial appendage. After cardiopulmonary bypass with moderate hypothermia is established, a left ventricular vent is placed via the right superior pulmonary vein. The ascending aorta is cannulated for administration of cardioplegia solution. The aorta is cross-clamped and cardioplegia solution is administered. A transverse aortotomy is performed after adequate arrest is achieved and the coronary ostia are identified. If the anomalous coronary ostium is located near the aortic valve commissure, take down of the commissure may be needed (Fig. 83-12). The anomalous ostium is opened longitudinally starting at the anomalous coronary os and continuing into the correct sinus (Fig. 83-13). A segment of the common wall between the aorta and coronary is excised and the intimal surfaces are approximated with interrupted sutures using 8-0 Prolene. If the commissure was taken down, it is resuspended with a pledgeted suture (Fig. 83-14). The aortotomy is then repaired and the cross-clamp is removed after de-airing. As the patient is rewarmed, close attention should be paid to the ECG to evaluate for signs of myocardial ischemia.

### CREATION OF A NEO-OSTIUM

The creation of a neo-ostium in the correct sinus is an alternate technique that may be used when the anomalous

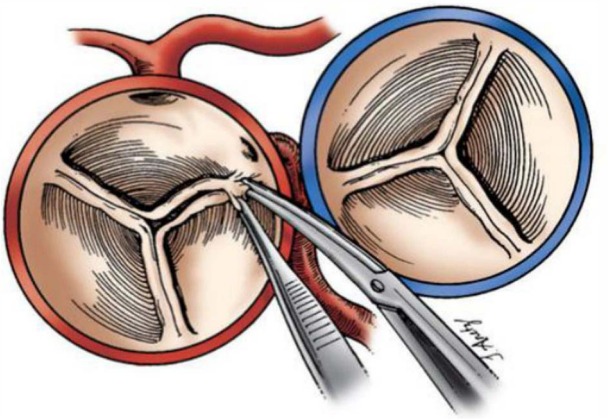


**FIGURE 83-12** When the coronary arises anomalously from the opposite sinus of Valsalva and courses between the pulmonary artery, the ostium is frequently abnormal. Repair may be undertaken by remodeling of the ostium. The abnormal ostium is usually located near a commissure and this commissure must be initially taken down to allow remodeling of the ostium. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

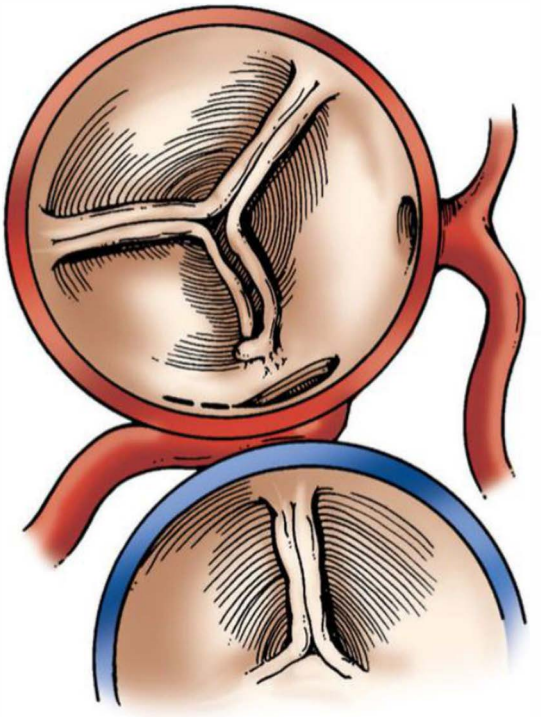


**FIGURE 83-13** After the commissure is detached, the abnormal coronary is incised longitudinally beginning at the abnormal ostium and this incision is carried into the right aortic sinus. A portion of the common wall between the aorta and coronary is excised. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

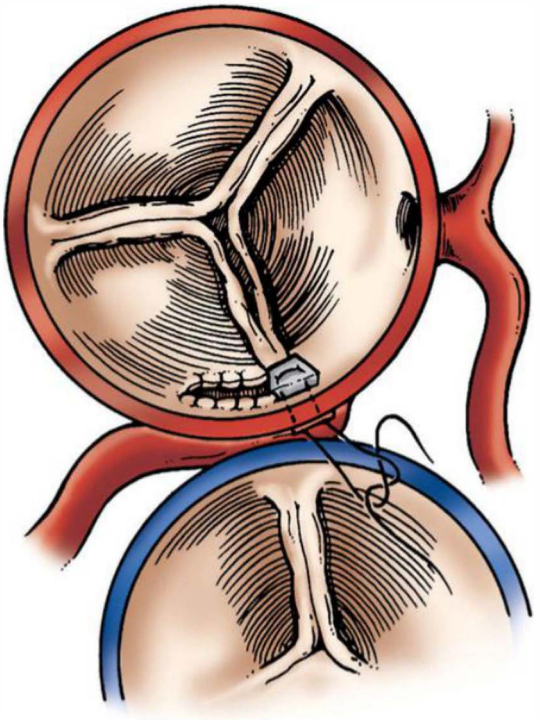


**FIGURE 83-14** The walls of the coronary artery and aorta are anastomosed with interrupted sutures of 8-0 polypropylene (Prolene), enlarging the ostium and preventing compression by the great vessels. The commissure of the aortic valve is resuspended with a pledgetted suture. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 1998.)

coronary passes intramurally below the aortic valve commissure. A probe is passed through the intramural segment of the anomalous coronary into the correct sinus. The coronary artery is opened where it exits the aorta and a neo-ostium is created. The intima is sewn to the aortic wall with interrupted sutures. This technique avoids the takedown and resuspension of the commissure.[51]

### OTHER TECHNIQUES

When there are two separate coronary ostia with an interarterial but not an intramural course, coronary artery translocation with reimplantation has been advocated.[62] This is similar to reimplantation done for the arterial switch procedure as described above for the ALCAPA repair. The coronary artery is excised with a button of aortic tissue and usually reimplanted above the commissure in the correct sinus. Since some believe that myocardial ischemia is due to coronary artery compression between the two great vessels, one technique that may be utilized when the anomalous coronary course is not intramural but the ostia are close together is pulmonary artery translocation. This technique has been used to possibly prevent the compression of the anomalous coronary artery is translocation of the MPA to the left pulmonary artery. This technique leaves the coronary circulation intact.[63] Combining coronary artery patch angioplasty using pericardium in addition to translocating the MPA to the left pulmonary artery has also recently been proposed.[64] Coronary artery bypass grafting utilizing saphenous vein or IMA grafts may be appropriate in the older adult; however, due to issues with long-term graft patency, this surgical option in children and young adults is generally not utilized.

## Surgical Results

No data exist regarding long-term neo-ostia patency rates in the unroofing procedure. However, short-to-mid-term results have overall been reassuring with no reports of ostial stenosis by echocardiography. In a study by Romp and colleagues, one patient developed severe aortic insufficiency requiring aortic valve replacement 44 months after the initial operation.[55] One study by Brothers and colleagues evaluated children in the short-to-mid-term following the unroofing procedure. They found subclinical evidence of myocardial ischemia in one-half of the patients with anomalous RCA and one of eight patients with anomalous left coronary artery, being asymptomatic during testing and having patent neo-coronary ostia by echocardiography.[33] The long-term clinical implications of these findings are unknown and further evaluation is needed over the next several years.

Although coronary artery reimplantation has been utilized by some, one study by Rinaldi and colleagues reported that two patients required subsequent emergency bypass grafting.[65] As this is an analogous procedure utilized for transposition of the great arteries, concern regarding long-term coronary patency may be warranted. A recent report by Pedra and associates evaluating children after repair of transposition of the great arteries demonstrated proximal eccentric intimal thickening by intravascular ultrasound in a majority of patients seen at least 5 years after the original surgery.[66] The long-term success of pulmonary artery translocation procedures is not known.

# CORONARY ARTERY FISTULA

A coronary artery fistula is an abnormal communication between a coronary artery and either a cardiac chamber or any of the great vessels, such as the coronary sinus, vena cavae, pulmonary artery, or a pulmonary vein.[67,68] Fistulas that end in right-sided structures, such as the right atrium, right ventricle, or pulmonary artery are termed arteriovenous fistulas while those that terminate in left-sided structures are described as arterioarterial fistulas.

Although coronary arterial fistulas comprise only 0.2 to 0.4 percent of congenital heart defects, they make up nearly half of all congenital coronary anomalies. They can be found in isolation, or in association with other forms of congenital

heart disease. Those that are acquired are the generally due to cardiac surgery, cardiac catheterization, or as a complication from Kawasaki disease.[69]

## Anatomy

Coronary artery fistulas may arise from either the right or the left coronary artery; occasionally both coronary arteries are affected.[70] The majority arises from an otherwise normal coronary artery. The fistulous connection may begin in the midportion of a coronary artery with a normal-sized vessel continuing beyond the fistula origin or the connection may arise as an end artery at the termination of the vessel. Proximal to the fistula, the coronary will be dilated and elongated proportionally to the size of the shunt across the fistulous connection. Distal to the fistula, the portion of the vessel usually returns to a normal diameter.

The right ventricle and the right atrium are the most common termination sites. In a review by Fernandes and colleagues, a single fistula was present in 83 patients and 10 had multiple fistulas.[71] The RCA was the most common site of origin and the right ventricle was the most common drainage site. Coronary fistulas were noted in 56 patients with otherwise normal cardiac anatomy while the others had additional cardiac lesions. Lowe and colleagues reviewed 286 patients and found the RCA to be the site of origin in approximately half of the patients and the left coronary artery system in nearly one-third.[72] Right-sided structures were the most common drainage sites (right ventricle 39 percent, right atrium 33 percent, and pulmonary artery 20 percent) with the left atrium or left ventricle in the remaining 8 percent.

## Pathophysiology

Coronary fistulas result in either a left-to-right or left-to-left shunt. The shunt is usually small to moderate when the fistula drains to the right side of the circulation; however, when the fistula drains into a left-sided chamber (i.e., left-to-left shunt), the result is an aortic runoff with similar physiology as aortic regurgitation. The shunt size is related to the amount of blood flow draining from the fistula to the chamber, as well as the chamber into which the fistula drains. Shunt size may also be affected by myocardial ischemia occurring from "steal" from the coronary circulation.

## Clinical Presentation

Patients with coronary artery fistula are usually asymptomatic and are rarely diagnosed in infancy or childhood. Many patients are diagnosed due to a murmur auscultated on exam that leads to an echocardiogram. The most common complaints if symptomatic are exertional dyspnea and fatigue. Angina is rare, even when coronary steal is present. Occasionally, a patient may present with ventricular dysfunction and congestive heart failure but this is more commonly seen in the adult. An older patient may present in atrial fibrillation due to right atrial enlargement caused by a coronary artery fistula to the right atrium.

On physical examination a continuous murmur is often heard. The murmur may be mistaken for a PDA but is heard lower on the sternal border, which is not the usual location for a PDA. In large left-to-left shunts a wide pulse pressure may be appreciated similar to aortic regurgitation.

### NATURAL HISTORY

In congenital coronary arterial fistulas, the fistula is present early in life and, over several years, gradually increases in size. Despite progressive enlargement of the coronary arteries, spontaneous rupture is rare. When rupture does occur, it is usually because of aneurysmal dilatation with weakening of the vessel wall due to a congenital defect or atherosclerosis. Bacterial endocarditis is possible due to the turbulent flow. Small fistulas may spontaneously close.

## Diagnostic Imaging

The ECG is commonly normal. However, it may demonstrate evidence of ventricular volume overload or atrial fibrillation, which may be seen in adult patients who have right atrial fistulous connections with subsequent chronic volume overload. Evidence of myocardial ischemia in the affected region may be noted if coronary steal is present. Chest radiography is usually normal but may show cardiomegaly or evidence of congestive heart failure. Giant aneurysms, if present, may also be noted. Two-dimensional echocardiography can show the fistulous origin, the chamber into which it drains, and any cardiac chamber enlargement and/or hypertrophy. Color Doppler should be used to demonstrate the fistula itself. MRI has become an excellent non-invasive imaging modality to diagnose and provide detailed anatomy of the coronary arterial fistula. Although it may replace cardiac catheterization, it currently is still used as an adjunctive imaging modality.

Cardiac catheterization with selective coronary angiography remains the gold standard. It is used in defining the coronary anatomy and the hemodynamic consequences of the fistula. An experienced interventional cardiologist may choose to coil embolize the fistula, alleviating the morbidities associated with cardiopulmonary bypass and sternotomy (Fig. 83-15).[73] However, the indications for coil embolization have not been well-defined in the pediatric population; therefore, the preferred treatment in most patients is surgical closure.[74]

## Surgical Management

### INDICATIONS FOR SURGERY

All patients with symptomatic coronary artery fistulas should undergo closure. Those who have very small fistulas may not require surgical closure; however, the natural progression of the fistula is to enlarge (Fig. 83-16), requiring close follow-up over time.[75] Asymptomatic patients with moderate-to-large fistulas should undergo elective surgical closure.

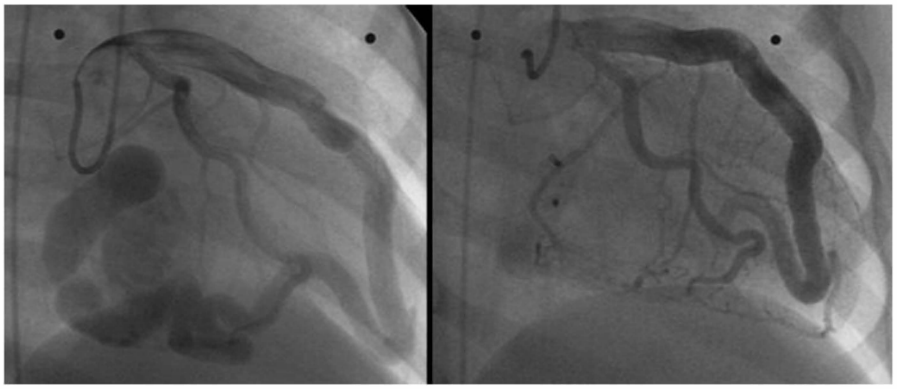


**FIGURE 83-15** Endovascular approach to large right coronary artery arteriovenous fistula (left). The fistulous tract was occluded percutaneously (right). (Courtesy of Dr. Richard Ringel, Division of Pediatric Cardiology, the Johns Hopkins Hospital.)

## SURGICAL TECHNIQUES

Coronary artery anatomy must be clearly defined, usually by coronary angiography, prior to surgical closure. Each operation should be individualized based on the anatomy. Often the fistula can be ligated or oversewn at its origin or termination without cardiopulmonary bypass; however, cardiopulmonary bypass should always be available.

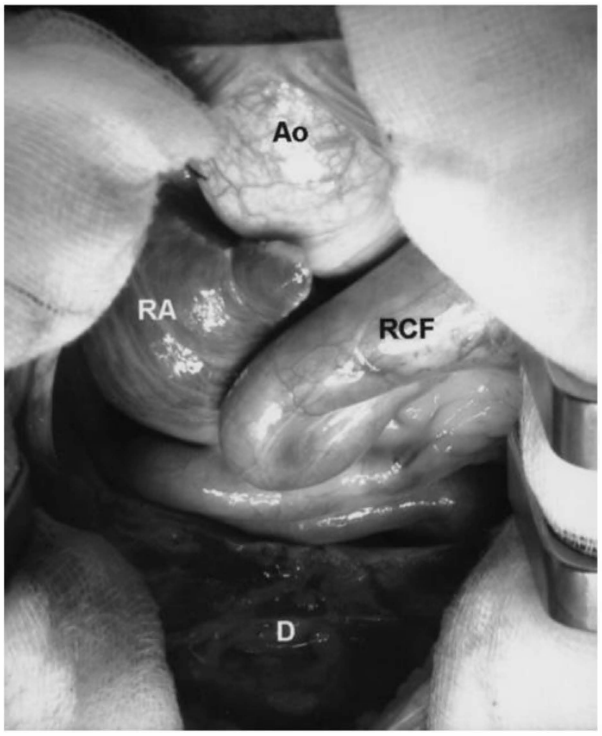



**FIGURE 83-16** Intraoperative photograph of giant right coronary artery arteriovenous fistula. The fistulous tract was ligated distally, before entrance in the right atrium. Ao, aorta; D, diaphragm; RA, right atrium; RCF, right coronary fistula. (Courtesy of Mr. Victor Tsang and Sir Magdi Yacoub, Cardiac Unit, Great Ormond Street Hospital for Children NHS trust, London.)

Through a median sternotomy the coronary anatomy is visualized and carefully inspected, noting the site of the enlarged vessel. When the fistula is located at the distal end of the coronary artery without viable myocardium distal to the fistula, it may be ligated without the use of cardiopulmonary bypass (Fig. 83-17). A ligature is placed around the coronary artery immediately proximal to the fistula, thus temporarily occluding the fistula. The heart is observed for signs of ischemia and the ECG is monitored closely. The ligature is tied if there is no evidence of ischemia and there is adequate myocardial perfusion. A second suture ligature should also be placed to ensure complete closure. Intraoperative transesophageal echocardiography may be useful to verify complete fistula closure.

Cardiopulmonary bypass is indicated under several conditions, including: the fistula originates from the middle of a coronary artery, the fistula is inaccessible, another cardiac lesion needs to be repaired during the operation, and/or the complete coronary course cannot be adequately delineated. The aorta and both cavae are cannulated and bypass is initiated. If cardioplegic arrest is necessary, the fistula should be temporarily compressed during administration of the cardioplegia to prevent runoff through the fistula into the heart. If adequate arrest is not possible due to flow through the fistula, it may be necessary to administer cardioplegia in a retrograde fashion.

Closing the fistula can be accomplished using a variety of techniques. If the fistula terminates in the middle of the LAD, the fistulous communication can be closed by placing multiple pledgeted sutures beneath the coronary artery, making sure to avoid compromising distal perfusion (Fig. 83-17). Coronary bypass grafting may be necessary if distal perfusion of the coronary bed is affected after closure of the fistula. Alternatively, when the fistula arises from the middle of the coronary artery, the latter can be opened longitudinally on the epicardial surface, oversewing the origin of the fistula from within the coronary arterial lumen (Fig. 83-18). The coronary artery can then be closed primarily.

If the right atrium or right ventricle is the site of the fistulous termination, it may be closed directly from within

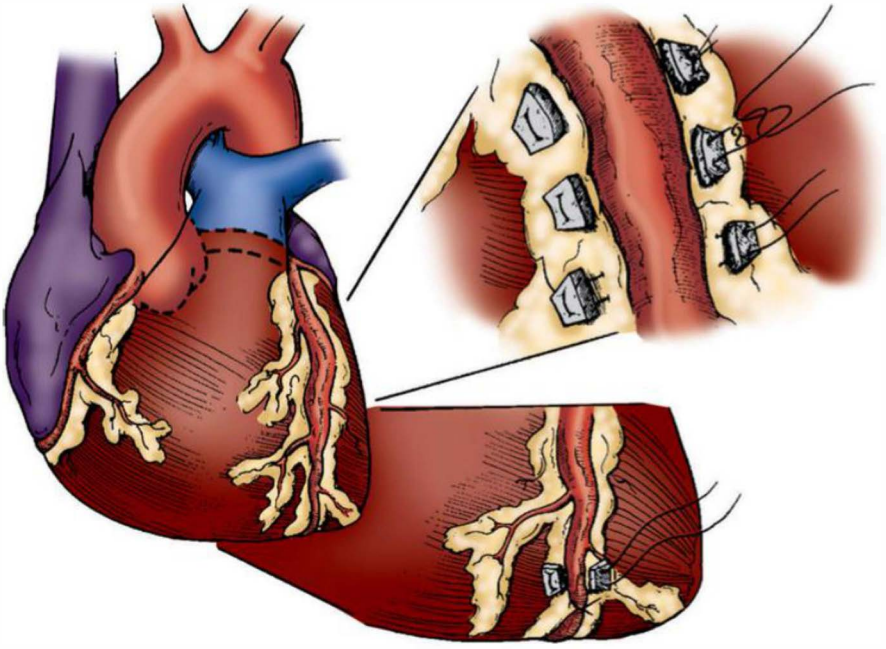


**FIGURE 83-17** If the termination site of the fistula is at the distal aspect of the coronary and no significant myocardium is in jeopardy, the coronary may be ligated proximal to the termination site. If the fistula terminates in the midportion of the left anterior descending coronary artery, the fistulous communication may be closed with multiple pledgetted sutures placed underneath the coronary artery so as not to impair distal perfusion. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

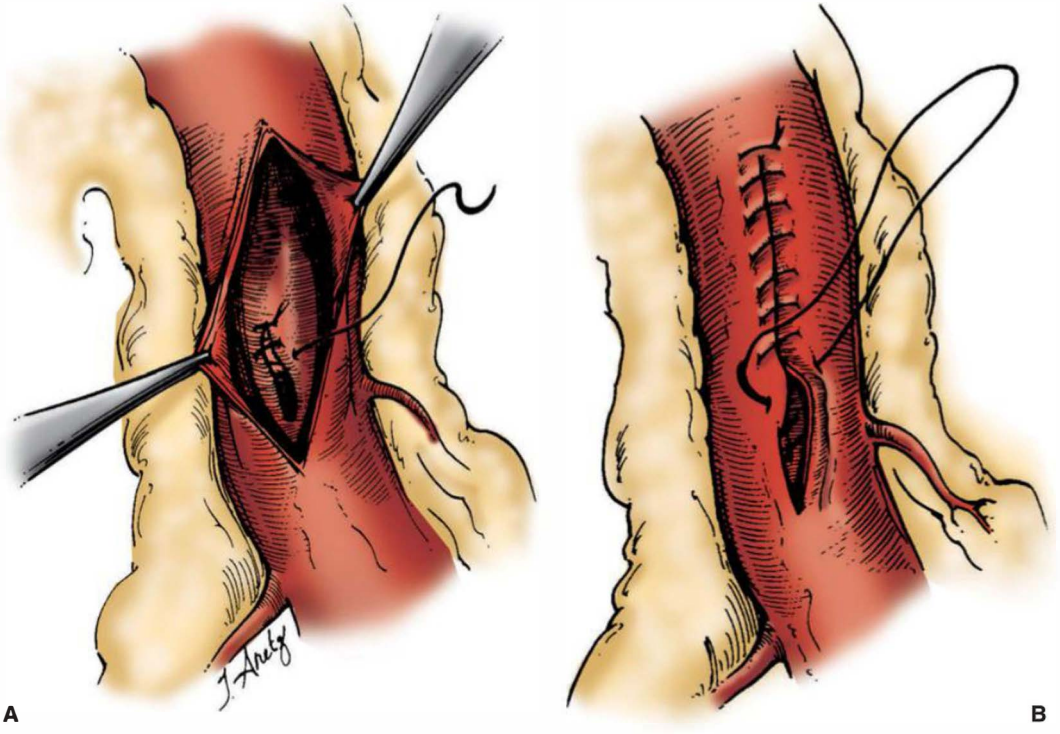



**FIGURE 83-18** **A.** When the fistulous communication arises from the midportion of the dilated coronary, the coronary may be opened longitudinally and the origin of the fistula oversewn from within the coronary. **B.** The coronary artery is closed primarily. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

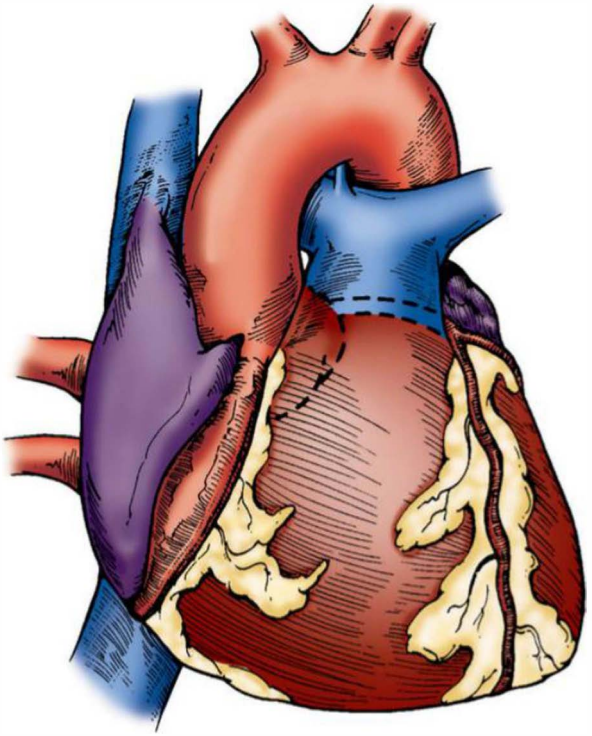


**FIGURE 83-19** A coronary arterial venous fistula arising from the midportion of the right coronary artery and terminating in the right atrium. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

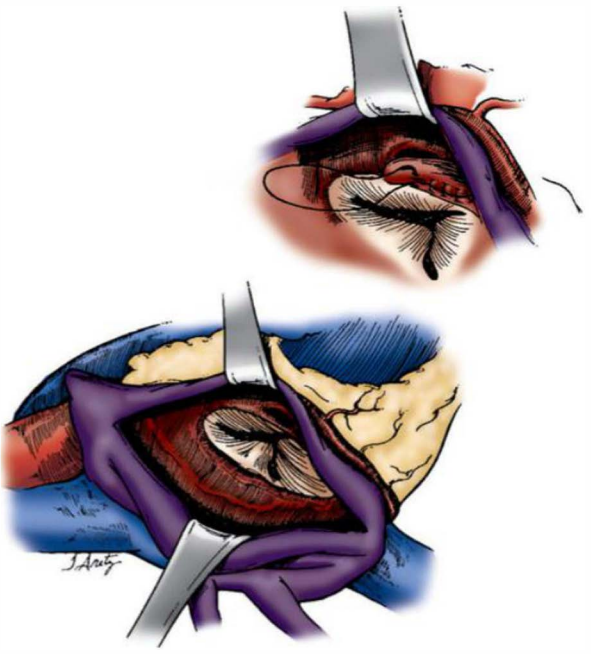


**FIGURE 83-20** After institution of cardiopulmonary bypass and induction of cardioplegia, the right atrium is opened and the termination site of the fistula identified from within the right atrium. This may be dosed primarily or with a patch of pericardium. (Reprinted with permission from: Gaynor JW. Coronary artery anomalies in children. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*. Philadelphia: Lippincott-Raven, 2007.)

the cardiac chamber (Fig. 83-19). After institution of cardiopulmonary bypass, a right atriotomy is performed and the termination site is noted from within the chamber. Cardioplegia may be useful for localization. The termination site may be closed primarily or with a pericardial patch (Fig. 83-20).

### SURGICAL RESULTS

The operative mortality for coronary artery fistula repair is very low and late results are excellent, with very few patients experiencing a recurrence.[52,70] In a report by Lowe and colleagues, 22 patients underwent surgical closure of coronary artery fistulas and four patients had the fistula closed using sutures without cardiopulmonary bypass.[72] In six patients, the fistula terminated within a cardiac chamber and was closed using cardiopulmonary bypass; in the remaining two patients, saphenous vein bypass grafts were necessary to maintain distal perfusion after fistula closure. There were no deaths at an average follow-up time of 10 years. One patient had a small residual fistula but there were no recurrences. Fernandes and colleagues reported no early or late mortality in 56 patients who had closure of isolated coronary artery fistula; however, two patients experienced a perioperative myocardial infarctions.[71] Finally, in a report by Mavroudis and colleagues on 17 pediatric patients (average age of 5.5 years), all had complete closure without recurrences or deaths.[74]

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## SURGERY FOR CONGENITAL CORONARY ANOMALIES BOARD REVIEW QUESTIONS (CHAPTER 83)

1. Which is correct regarding anomalous origin of a coronary artery from the pulmonary artery (ALCAPA)?
   A. The most common form is the right coronary artery arising from the pulmonary artery
   B. It is the most common cause of myocardial infarction in childhood
   C. An anomalous left main coronary artery typically arises from the anterior sinus of the main pulmonary artery
   D. Diagnosis is usually evident at birth
   E. A shunt will develop, resulting in coronary-pulmonary steal

2. Which is true for surgical repair of ALCAPA?
   A. Surgery should be delayed for 4–6 weeks to allow for myocardial recovery
   B. Infants with severe LV dysfunction and mitral insufficiency should be considered for cardiac transplantation
   C. Mitral valve repair with or without LV aneurysmectomy is indicated for concomitant severe mitral insufficiency
   D. Left internal mammary artery bypass grafting is the gold standard for children
   E. The classic Takeuchi operation uses a portion of the anterior wall of the pulmonary artery for coronary baffling

3. Which is true regarding outcomes after surgical repair of ALCAPA?
   A. Coronary ligation is associated with a 25% late mortality rate
   B. Left ventricular function is normal in 75% of patients after coronary transfer
   C. Over 50% of patients will have moderate or greater mitral insufficiency at late follow-up
   D. In adults, the preferred technique has become direct coronary reimplantation
   E. Early surgical repair of mitral insufficiency is generally necessary, as late repair is more difficult and less likely to be successful in a child

4. Which of the following is not an appropriate operation for anomalous coronary artery between the aorta and pulmonary artery diagnosed in a child?
   A. Unroofing procedure
   B. Creation of a neo-ostium
   C. Coronary artery translocation
   D. Pulmonary artery translocation
   E. Coronary artery bypass grafting
5. Which is true regarding coronary artery fistulas?
   A. The majority arise from a diseased artery
   B. The coronary artery will be dilated and elongated distal to the fistula
   C. The left ventricle and the right atrium are the most common termination sites
   D. A coronary fistula can cause either a right-to-left or a left-to-right shunt
   E. The most common presentation is angina

## ANSWERS

1. **Answer: B.** ALCAPA is the most common cause of myocardial infarction in childhood. The most common form is left main coronary artery arising from the pulmonary artery, originating from the posterior sinus of the main pulmonary artery. Diagnosis usually is not made until after ductal closure and pulmonary resistance falls, resulting in a pulmonary-coronary steal.
2. **Answer: E.** The classic Takeuchi operation uses a portion of the anterior wall of the pulmonary artery for coronary baffling. Surgery should be performed promptly to prevent further myocardial ischemia. Significant myocardial recovery will occur; therefore, transplantation and mitral operations are rarely indicated. Coronary artery bypass grafting is rarely used for this condition in children.
3. **Answer: A.** Coronary ligation is associated with a 25% late mortality rate. LV function is normal is about 90% of patients after coronary transfer, and nearly 85% have only mild mitral insufficiency. In adults, the preferred technique is coronary artery bypass grafting. Early surgical repair of mitral insufficiency is generally not necessary, as late repair is technically simpler and more likely to be successful in a child.
4. **Answer: E.** Coronary artery bypass grafting is generally not indicated in children, as long-term patency may be unsatisfactory. The remaining operations have all been demonstrated to achieve excellent results.
5. **Answer: D.** A coronary fistula can cause either a right-to-left or a left-to-right shunt, depending on drainage patterns. The majority arise from an otherwise normal coronary artery. The coronary artery will be dilated and elongated proximal to the fistula. The right ventricle and the left atrium are the most common termination sites. Most patients are asymptomatic on presentation and are diagnosed with a murmur.

84

# Vascular Rings and Pulmonary Artery Sling

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**KEY CONCEPTS**

- Epidemiology
  - Vascular rings and pulmonary artery sling (PAS) represent 1 to 3 percent of all congenital cardiac malformations. The most frequent type of vascular ring is aberrant left subclavian artery, whereas the most rare condition is the PAS.
- Morphology
  - Of the over 100 variations in morphology that have been described, 6 are most commonly observed: (1) anomalous left subclavian artery with left aortic arch, (2) double aortic arch (DAA), (3) right aortic arch with left ligamentum, (4) right aortic arch with aberrant left subclavian artery, (5) tracheal compression by the innominate artery, and (6) PAS. Cardiac malformations (tetralogy of Fallot, ventricular septal defect, atrial septal defect, and aortic coarctation) are seen in 15 to 20 percent of cases.
- Pathophysiology
  - Structural obstruction of the aerodigestive tract
- Clinical features
  - Most vascular rings are symptomatic. Compression by the complete or partial ring of the esophagus, trachea, or both dictates the mode of presentation. Patients with an aberrant left subclavian artery are often asymptomatic, whereas pulmonary artery sling and complete rings are almost uniformly clinically significant.
- Diagnosis
  - Chest x-ray is rarely diagnostic. Barium esophagography is usually able to point to the presence of a vascular ring with reasonable specificity. Computed tomography (CT) and magnetic resonance imaging (MRI) are useful in defining the anatomy and are currently more routinely utilized. Bronchoscopy is important in the diagnosis of both innominate artery compression and PAS and in assessing the degree of tracheobronchomalacia.
- Treatment
  - Treatment is indicated in all symptomatic patients. With the exception of DAA with dominant left component, almost all cases (left aortic arch with right ligamentum, PAS, and innominate artery compression) are approached through a left thoracotomy with division of the vascular ring.
- Outcomes
  - For the vast majority of vascular rings, morbidity and mortality are the same as seen in any simple thoracic procedure involving a thoracotomy. Mortality is much higher for patients with PAS. The degree of tracheobronchomalacia has a significant impact on long-term prognosis.

## INTRODUCTION AND DEFINITIONS

Vascular rings are congenital abnormalities of the aortic arch system that cause tracheal and esophageal compression. Patients with vascular rings have varying degrees of symptoms that range from subtle swallowing difficulties in the adolescent to severe respiratory distress in the neonate. The symptoms depend on the tightness of the vascular ring as it compresses the esophagus and/or trachea. The phrase "pulmonary artery sling (PAS)" refers to a particular anomaly where the left pulmonary artery (PA) originates from the right PA and compresses the distal trachea and right bronchus on its route to the left lung. The Congenital Heart Surgery Nomenclature and Database Project Committee has standardized the classification of vascular rings to include complete rings [double aortic arch (DAA), right aortic arch

with left ligamentum] and incomplete rings [pulmonary artery sling (PAS), innominate artery compression].[1] Each of these vascular rings can have different anatomic variations. Nearly all patients with complete vascular rings and PAS will eventually require surgical intervention. Although the literature now contains citations describing over 100 variations of vascular rings, in this chapter we will focus on the most common vascular rings. We will also address the issue of a Kommerell diverticulum and select rare vascular rings. We will review the historic surgical events in vascular ring surgery, the epidemiology, embryology, pathogenesis, the clinical presentations and diagnostic evaluations, the surgical management, and postoperative care and outcomes.

## HISTORY

The first vascular ring described in the medical literature involved a patient with a DAA described by Hommel in 1737.[2] The first surgical repair of a vascular ring was performed by Robert Gross on a patient with a DAA in 1945.[3] In his report, Gross coined the term "vascular ring." Gross also reported the first repair of a right aortic arch with left ligamentum, and innominate arteriopexy for innominate artery compression syndrome.[4] Willis J. Potts from Children's Memorial Hospital (Chicago) was the first to successfully repair a PAS in 1953.[5]

## EPIDEMIOLOGY

Because some patients with vascular rings fail to manifest symptoms, the exact prevalence of this anomaly is not truly known. In one comprehensive series, the estimate ranged from 0.04 to 0.5 percent of live births or approximately 1 to 3 percent of surgical congenital cardiovascular anomalies.[6] The most common vascular anomaly is left aortic arch with an aberrant (retroesophageal) right subclavian artery (not a complete vascular ring) with a prevalence of 0.5 percent.[7] In a comprehensive cardiovascular screening program using echocardiography in school-age children, Chen and colleagues reported the following incidence of vascular rings in 186,213 screened children: PA sling ($n = 11$, 0.006 percent), anatomically complete vascular ring (DAA, right aortic arch with left ligamentum, $n = 96$, 0.05 percent).[8,9]

## EMBRYOLOGY AND PATHOGENESIS

There is a fascinating and surgically important relationship between the embryology and clinical anatomy of vascular ring anomalies. The characterization of the embryonic arch system by Edwards is based on a hypothetical intermediate stage involving an initial DAA in all patients that progresses in most cases to a single arch system (Fig. 84-1).[10]

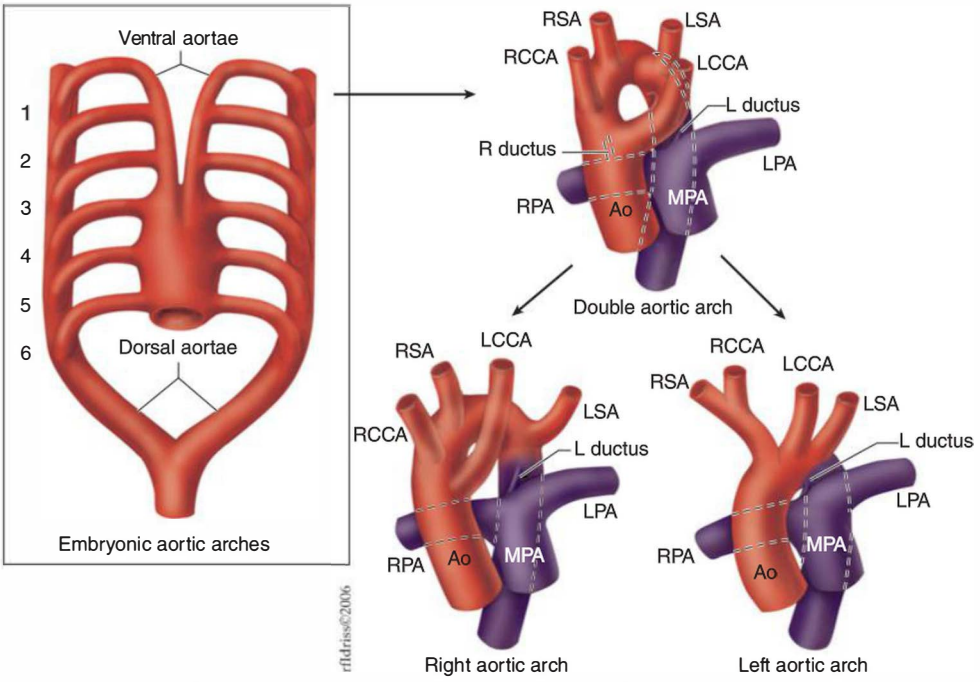



**FIGURE 84-1** Embryonic arotic arch development. Diagram of the embryonic aortic arches with six pairs of aortic arches originally developing between the dorsal and ventral aorta. During development, the first, second, and fifth arches regress. Preservation or deletion of different segments of the other arches results in either a double aortic arch, a right aortic arch, or the "normal" left aortic arch. Ao, aorta; CCA, common carotid artery; L, left; PA, pulmonary artery; R, right; SA, subclavian artery. (Reprinted with permission from Mavroudis C. *Pediatric Cardiac Surgery*, 3rd edition. Philadelphia: Mosby Elsevier, 2003.)

Initially, an aortic arch is located on either side of the trachea with a ductus arteriosus on each side. In this system, early in development six pairs of arches are present that connect the ventral and dorsal aorta. During further development, these arches variously mature, recede, fuse, and remodel to eventually form the typical left-sided aortic arch. Different vascular rings form when specific segments of the aortic arches either persist or resorb. During normal development, most of the first, second, and fifth arches regress, and the third arch persists to become the carotid artery. The right fourth arch forms the right brachiocephalic artery. The left fourth aortic arch becomes the ascending aorta and transverse aortic arch. The fifth aortic arch regresses on each side. In the typical left arch patient, the right dorsal portion of the sixth arch regresses, and on the left side it persists as the ductus arteriosus. The PA forms from a branch of the ventral bud of the sixth aortic arch which connects to the lung bud. The seventh intersegmental artery matures into the subclavian artery. The sidedness of the aortic arch is determined by which fourth arch persists which usually is the left. The anatomic definition of a left arch is that the apex of the aortic arch is to the left of the trachea. With reference to the center of the vertebral bodies, the descending aorta may be either right, left, or midline.

## DOUBLE AORTIC ARCH

A DAA forms when the ascending aorta arises normally from the heart but as it exits the pericardium, the right and left arches both persist and encircle the esophagus and trachea (Figs. 84-2 and 84-3). The left aortic arch passes anterior to the trachea and connects to the descending aorta at the level of the ligamentum arteriosum, while the right aortic arch courses posteriorly to the trachea and esophagus and then joins the descending aorta. The right arch typically gives rise to the right carotid and right subclavian arteries; the left subclavian and carotid arteries originate from the left aortic arch. In our series the right-sided (posterior) arch was dominant in 75 percent of patients with a DAA, the left-sided (anterior) arch was dominant in 18 percent of the patients, and the arches were equal in size in 7 percent of the patients.[11]

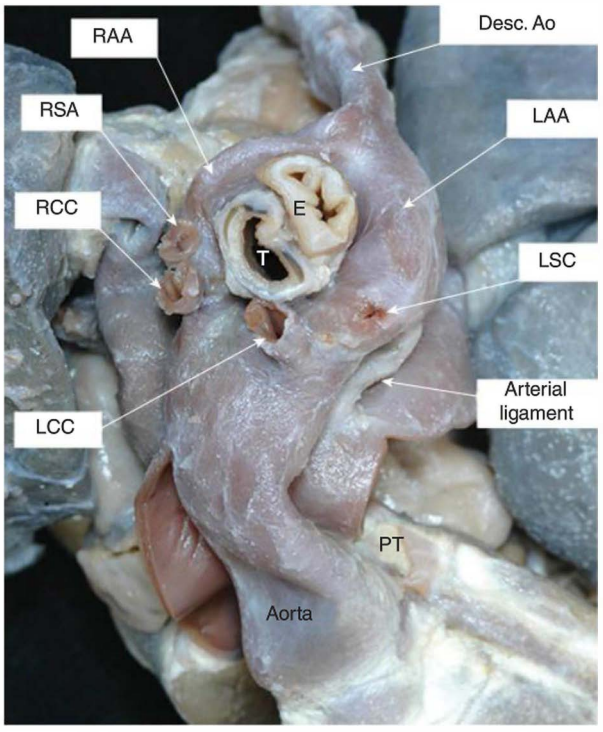



**FIGURE 84-2** Double aortic arch. Autopsy specimen of a child with a double aortic arch (left arch dominant). Desc. Ao, descending aorta; E, esophagus; LAA, left aortic arch; LCC, left common carotid; LSC, left subclavian; PT, pulmonary trunk; RAA, right aortic arch; RCC, right common carotid; RSA, right subclavian artery; T, trachea. (Courtesy of Diane Spicer from the F.S. Idriss Registry, Children's Memorial Hospital, Chicago, IL.)

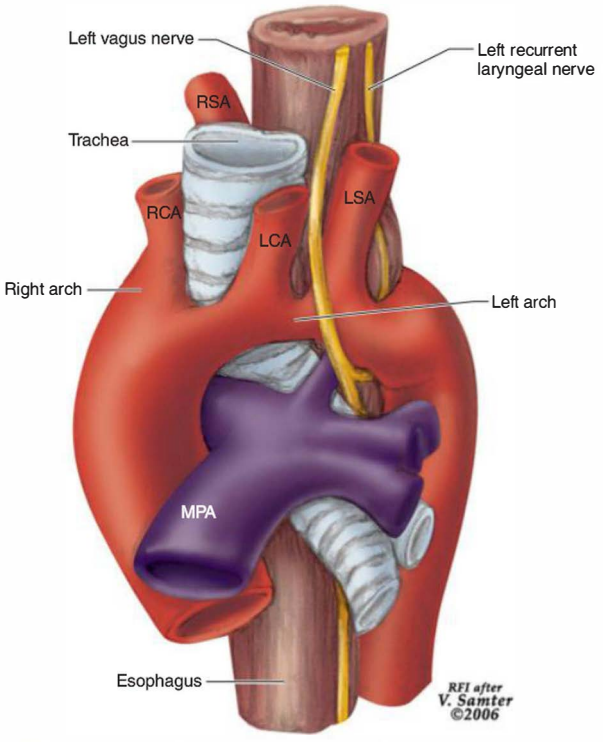



**FIGURE 84-3** Double aortic arch. This is an illustration of a dominant right arch with a smaller but patent left arch with separate origins of the right and left carotid and subclavian arteries. (RCA, right carotid artery, RSA, right subclavian artery, LCA, left carotid artery, LSA, left subclavian artery, MPA, main pulmonary artery.) (From Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: Vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds). *Pearson's Thoracic and Esophageal Surgery.* Philadelphia: Churchill Livingstone Elsevier, 2008:242–255.)

## RIGHT AORTIC ARCH WITH LEFT LIGAMENTUM

A right aortic arch (RAA) occurs when the left fourth arch involutes and the right fourth arch persists. The two anatomic types of right aortic arch are classified based on the branching pattern of the arch vessel as: retroesophageal left subclavian artery (Fig. 84-4) and mirror-image branching (left brachiocephalic artery) (Fig. 84-5).[12] In our series this distribution was 66 percent retroesophageal left subclavian artery and 34 percent mirror-image branching.[11] A complete vascular ring occurs when the ligamentum arteriosum connects the descending thoracic aorta to the PA. The vascular ring configuration includes the right aortic arch, the PA, and the ligamentum. In the patient with a retroesophageal left subclavian artery, the ligamentum arteriosum nearly always comes from the descending aorta, completing the vascular ring. In the patient with mirror-image branching, the ligamentum arteriosum may arise either from the descending thoracic aorta or the anterior left brachiocephalic artery. If the ligamentum arises from the left brachiocephalic artery a vascular ring is not formed (Fig. 84-6). This is the common situation in patients with tetralogy of Fallot and truncus arteriosus.

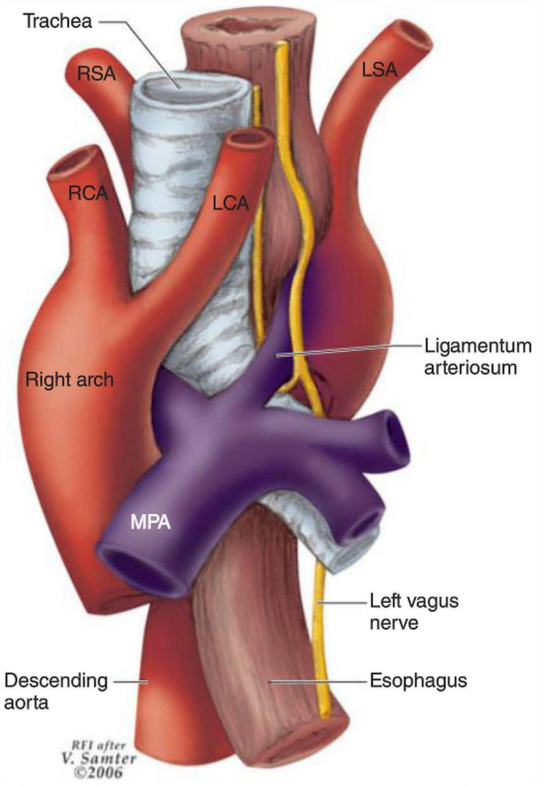



**FIGURE 84-4** Right aortic arch, left ligamentum, retroesophageal left subclavian artery. The vascular ring is formed by the right aortic arch, the main pulmonary artery, and the ligamentum arteriosum (RCA, right carotid artery; RSA, rigth subclavian artery; LCA, left carotid artery; LSA, left subclavian artery; MPA, main pulmonary artery). (From: Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: Vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds). *Pearson's Thoracic and Esophageal Surgery*. Philadelphia: Churchill Livingstone Elsevier, 2008:242–255.)

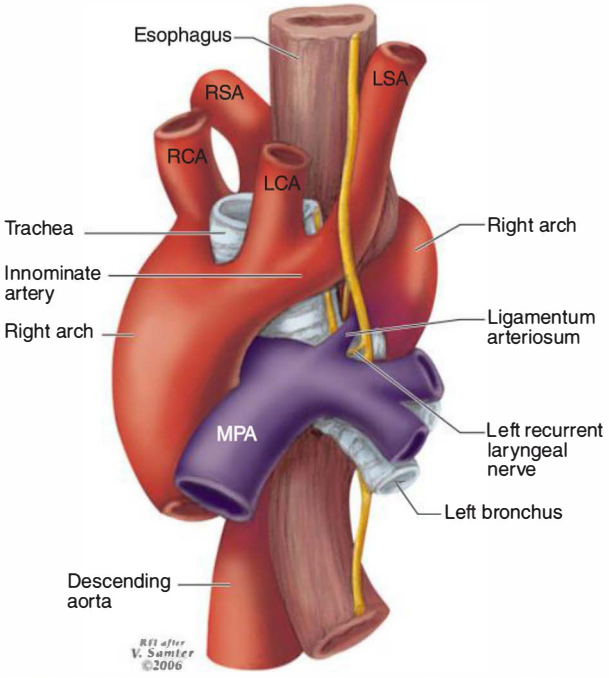



**FIGURE 84-5** Right aortic arch, left ligamentum, mirror-image branching (Note left innominate artery). The vascular ring is formed by the same components as in Figure 84-3, but the left subclavian artery has an anterior origin from the left innominate artery. (RCA, right carotid artery; RSA, right subclavian artery; LCA, left carotid artery; LSA, left subclavian artery; MPA, main pulmonary artery; Innominate A, innominate artery.) (From Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: Vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds). *Pearson's Thoracic and Esophageal Surgery*. Philadelphia: Churchill Livingstone Elsevier, 2008:242–255.)

## INNOMINATE ARTERY COMPRESSION

Innominate artery compression results when the anterior trachea is depressed by the innominate artery as it travels from left to right within the superior mediastinum. The exact mechanism that causes the aortic compression in some patients is unknown but may involve a more distal takeoff of the innominate artery from the aorta or a predisposition to tracheomalacia. Figures 84-7–84-9 show by computed tomography (CT) imaging how the tracheal

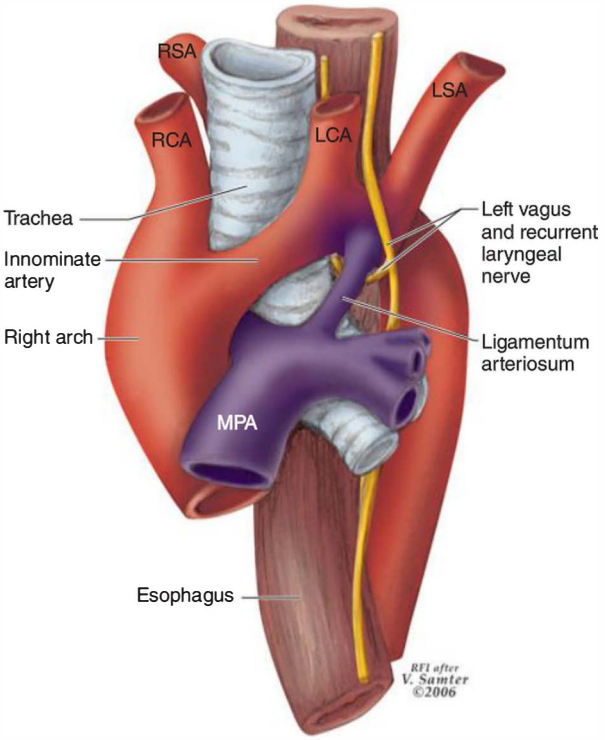
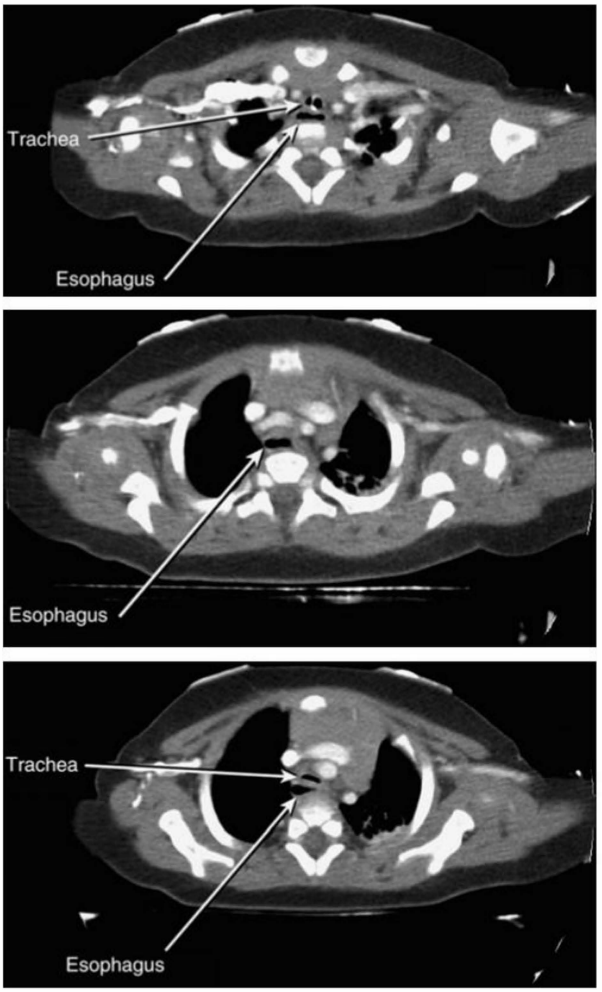



**FIGURE 84-6** Right arch, mirror-image branching with ligamentum from innominate artery. There is a space between the ligamentum and descending aorta and a vascular ring is *not* formed. (RCA, right carotid artery; RSA, right subclavian artery; LCA, left carotid artery; LSA, left subclavian artery; MPA, main pulmonary artery; Innominate A, Innominate artery.) (From Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: Vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds). *Pearson's Thoracic and Esophageal Surgery.* Philadelphia: Churchill Livingstone Elsevier, 2008:242–255.)




**FIGURES 84-7–84-9** Innominate Artery Compression Syndrome. Serial CT cuts in a 5-month-old infant with severe stridor. The tracheal lumen completely disappears in the second of the three images. By bronchoscopy the lumen was nearly occluded. The child responded very well to innominate arteriopexy. (From Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: Vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds). *Pearson's Thoracic and Esophageal Surgery.* Philadelphia: Churchill Livingstone Elsevier, 2008:242–255.)

lumen can be compressed in a 5-month old with severe stridor from innominate artery compression syndrome.

## PULMONARY ARTERY SLING

PAS occurs when two embryologic abnormalities coexist at the same time. The left PA originates from the right sixth arch instead of the left sixth arch and the course of the left PA is posterior rather than anterior to the maturing tracheobronchial tree. The anatomic result is that the left PA originates from the posterior aspect of the right PA and not from the main PA (Fig. 84-10). The left PA then courses posteriorly over the right main stem bronchus and then between the trachea and esophagus which results in a sling compressing the right main stem bronchus and the posterior distal trachea. The ductus or ligamentum originates from the usual site on the main PA and connects to the aorta. A true vascular ring does not exist but the "sling" causes significant symptomatic compression. There is a strong association between PAS and complete cartilage tracheal rings causing tracheal stenosis.[13]

## ABERRANT RIGHT SUBCLAVIAN ARTERY WITH A LEFT AORTIC ARCH

This lesion is not a true vascular ring but is the most common vascular arch anomaly, occurring in 0.5 percent of all humans (Fig. 84-11).[7,14] In this anomaly the aortic arch and descending thoracic aorta are left-sided, and there is no right brachiocephalic artery present. The right subclavian artery

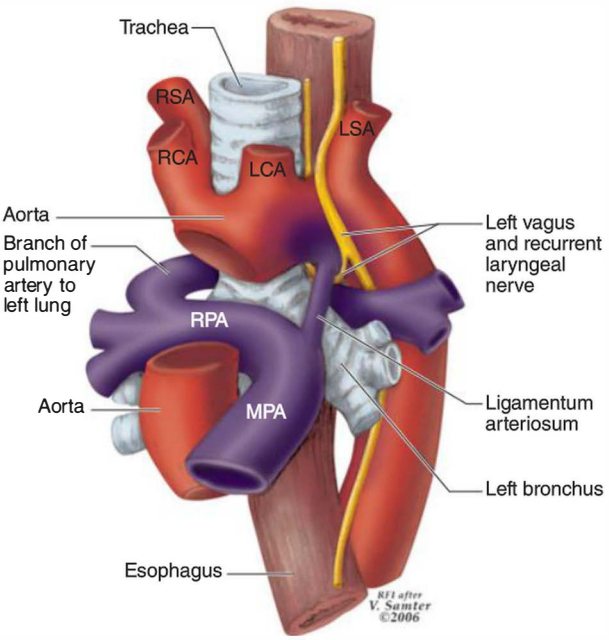



**FIGURE 84-10** Pulmonary artery sling. The aorta has been cut away to visualize the right pulmonary artery and the anomalous origin of the left pulmonary artery from the rigth pulmonary artery. The left pulmonary artery courses posterior to the trachea, anterior to the esophagus, and anterior to the descending thoracic aorta on its way to the left lung. (RCA, right carotid artery; RSA, right subclavian artery; RPA, right pulmonary artery; LCA, left carotid artery; LSA, left subclavian artery; MPA, main pulmonary artery; Innominate A = Innominate artery.) (From Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: Vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds). *Pearson's Thoracic and Esophageal Surgery.* Philadelphia: Churchill Livingstone Elsevier, 2008:242–255.)

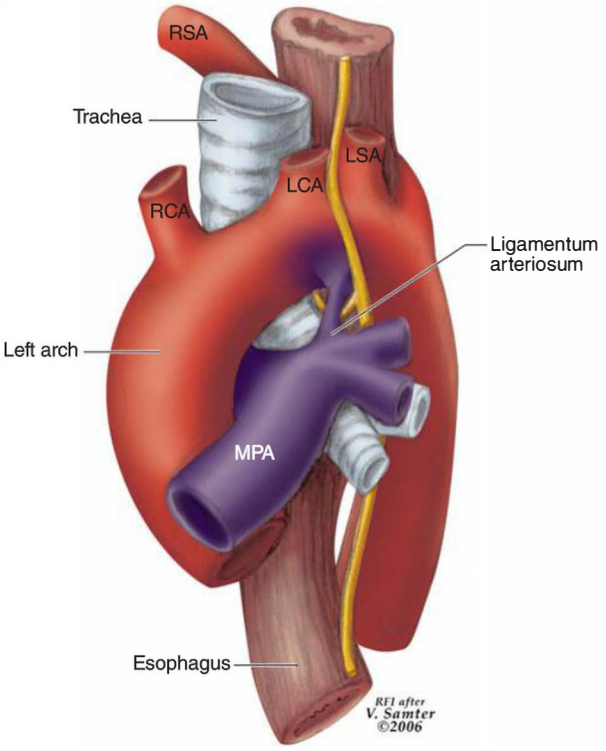



**FIGURE 84-11** Aberrant right subclavian artery. This illustration is a right subclavian artery originating from the descending thoracic aorta distal to the take-off of the left subclavian artery. This artery courses in the posterior mediastinum posterior to the esophagus as it travels to the rigth arm. (RCA, right carotid artery; RSA, rigth subclavian artery; LCA, left carotid artery; LSA, left subclavian artery; MPA, main pulmonary artery.) (From Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: Vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds). *Pearson's Thoracic and Esophageal Surgery*. Philadelphia: Churchill Livingstone Elsevier, 2008:242–255.)

arises independently from the descending thoracic aorta and traverses the mediastinum posterior to the esophagus en route to the right arm. This lesion in fact rarely (if ever) causes symptoms and surgical intervention for these patients is uncommon.[15] We have not operated on a patient with this diagnosis since 1973. What frequently occurs is that, during the evaluation of a patient with swallowing symptoms, an aberrant right subclavian artery is discovered and mistakenly considered as the etiology of the swallowing symptoms. That is why this is referred to as "dysphagia lusoria" which refers to difficulty in swallowing due to a "trick of nature."[15] The aberrant right subclavian artery and swallowing difficulties are "true, true, and unrelated." The exception to the usual recommendation of no surgical intervention is the older patient with aneurysmal dilation of the origin of the right subclavian artery, a Kommerell diverticulum.[16] These patients may indeed require Kommerell diverticulum resection and right subclavian artery reimplantation, usually in the older adult patient.[17]

## RARE VASCULAR RINGS

Since many embryonic variants may exist, there are numerous rare vascular ring anomalies that have been reported.[18–22] One rare vascular ring is created by a left aortic arch, right descending thoracic aorta, and a right ligamentum arteriousum.[21] A second rare vascular ring involves a right aortic arch, right ligamentum, and an absent left PA.[18] Another rare vascular ring is a circumflex aorta that consists of a right aortic arch, a left-sided descending thoracic aorta, and left ligamentum arteriosum.[22] In this lesion the problem is posterior compression of the trachea by the aorta crossing from right to left above the carina.

## ASSOCIATED ANOMALIES

The most commonly associated lesion in patients with vascular rings is congenital heart disease, occurring in 12 percent of patients with vascular rings.[11] The most common cardiac

lesions are ventricular septal defect and tetralogy of Fallot. The most commonly associated chromosomal abnormality is 22q.11 deletion, which occurs in 15 to 20 percent of patients with associated cardiac defects.[23] These additional anomalies can impact the operative strategy, the postoperative recovery period, and the long-term outcome for these patients.

## CLINICAL SYMPTOMS

The severity of symptoms from a vascular ring are directly correlated with the degree of compression of the trachea and esophagus. Clinical symptoms vary with the age of the patient. Symptoms in neonates primarily derive from tracheal compression, while dysphagia occurs later in life when the child is transitioning to solid food. The common symptoms from tracheal compression are a barky cough, stridor, wheezing, recurrent respiratory infections, respiratory distress, and apnea.[11] Patients with a DAA present earlier in life than patients with a right aortic arch because they have a tighter ring. Patients with innominate artery compression syndrome typically present in the first 3 to 6 months of life. PAS can present from newborn to adult, but most commonly in the first year of life. Since vascular rings are such a rare condition, patients are often initially misdiagnosed with more common etiologies of respiratory illnesses, such as asthma, croup, and reflux. The diagnosis is dependent on the clinician having a high index of suspicion.

As the infant transitions from liquids to solids, poor feeding may result with episodes of choking from compression of the esophagus. Other patients go for many years without swallowing issues despite severe compression and finally present for unknown reasons as adults. Each of the different vascular rings can cause certain symptoms due to their anatomical compression of the trachea or esophagus. For instance, PAS and innominate artery compression syndrome do not cause dysphagia, but can cause apnea.

## DIAGNOSIS

The diagnosis of a vascular ring initially starts with a detailed history and physical examination with careful attention being paid to potential symptoms related to the compression of the esophagus and trachea. A thorough history is sometimes needed to reveal the subtle clinical symptoms that occur with these patients. This is then followed with a diagnostic study to confirm the diagnosis. Possible diagnostic studies employed include: chest x-ray, barium esophagram, bronchoscopy, echocardiogram, CT, and magnetic resonance imaging (MRI). Barium swallow used to be the primary means of diagnosis but is now rarely used. Cardiac catheterization is no longer used as a diagnostic study for patients with vascular rings. Echocardiography is used mostly to rule out other congenital heart anomalies and not to establish a diagnosis of vascular ring, except in the situation of a PAS. The main studies we and others now recommend are either CT or MRI which clearly defines the anatomy of the vascular ring and allows operative planning.[11,24,25]

The first study is the chest x-ray which serves two purposes. First, it rules out other etiologies of respiratory problems such as pneumonia or an aspirated foreign body. Second, the chest x-ray defines the location of the aortic arch. The presence of an aortic "knob" on the right side compressing the lateral wall of the trachea lends strong suspicion to a DAA or right aortic arch. Although the barium esophagram may show indentations in the esophagus from the vascular ring, it does not give a precise diagnosis or surgical roadmap. However, a normal barium esophagram does rule out a DAA or a right aortic arch with a left ligamentum. PAS is the only vascular ring that causes anterior compression of the esophagus on a barium esophagram but this can sometimes be subtle and difficult to recognize. We have essentially abandoned barium esophagram in the diagnosis of vascular rings.[11]

If the suspicion for a vascular ring is high, a CT scan or MRI is the next preferred study. We prefer CT over MRI for several reasons. First, the CT scan using the new multislice, multidetector technology obtains the images in a faster period of time which is very useful in a patient with a compromised airway.[11] The CT scan may take 30 s to obtain in contrast to the MRI scan which may take 30 to 45 min. Small children and infants may find it difficult to stay still for this long which makes it challenging to obtain good images. CT also provides better evaluation of the central airways and lung parenchyma.[24] Lastly, three dimensional (3D) reconstructions from the CT scan images provide a detailed relationship of the vascular rings with the other mediastinal structures, necessary for operative planning.[25]

The CT scan has findings that are specific to each of the individual vascular rings. One typical sign is the "four artery sign" which may be seen on coronal sections superior to the aortic arch (Fig. 84-12). The four arteries are the two dorsal subclavian arteries and the two ventral carotid arteries that are symmetrically spaced around the trachea in a patient with a true complete vascular ring. This arrangement of the four

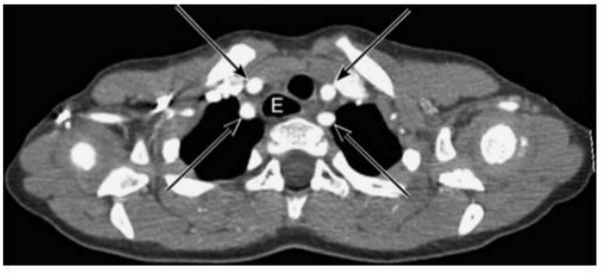



**FIGURE 84-12** "Four-artery" sign. CT scan of a 3-year-old child with a right aortic arch with left ligamentum. Note the four brachiocephalic vessels grouped symmetrically around the trachea. Also note the dilated proximal esophagus (E). (From Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: Vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds). *Pearson's Thoracic and Esophageal Surgery*. Philadelphia: Churchill Livingstone Elsevier, 2008:242–255.)

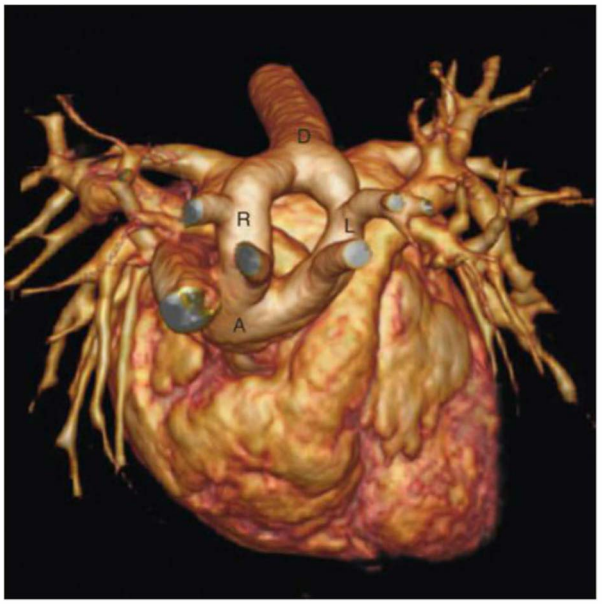



**FIGURE 84-13** Double aortic arch, both arches patent. CTA Chest: 3D Reconstruction. This is a view looking down from above at a double aortic arch with the distal left arch being slightly smaller than the right arch. A, ascending aorta; D, descending aorta; L, left aortic arch; R, right aortic arch. (Courtesy of Cynthia Rigsby, MD, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL.)

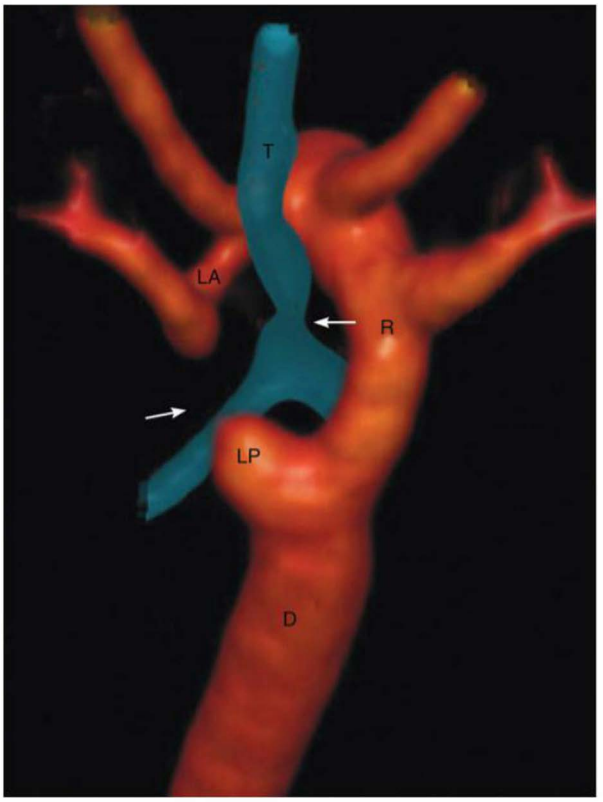



**FIGURE 84-14** Double aortic arch, atretic distal left arch. CTA Chest: 3D Reconstruction. This is a posterior view of the aortic arch in a patient with a right dominant double aortic arch. The distal left aortic arch is atretic. The large arrow shows where the ligamentum and distal arch were located at the time of surgery. Smaller arrow shows tracheal compression by the vascular ring. The distal left arch is a bulbous remnant of the left fourth arch. D, descending aorta; LA, anterior left aortic arch; LP, posterior left aortic arch; R, right aortic arch; T, trachea.(Courtesy of Cynthia Rigsby, MD, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL.)

arteries is seen in both DAA and in right aortic arch with a left ligamentum and retroesophageal left subclavian artery. The breakthrough from a surgical standpoint in imaging is the 3D reconstruction possible with CT and MRI. Examples are shown in Figures 84-13 and 84-14. The exquisite detail provided leaves little doubt about the most effective surgical approach and management. In patients with innominate artery compression syndrome, CT demonstrates anterior compression of the trachea (Figs. 84-7, 84-8, and 84-9). In patients with a PAS, CT shows the anatomic origin of the left PA from the right PA and its course between the trachea and esophagus (Figs. 84-15 and 84-16). It is also very useful to evaluate the trachea in these patients. One limitation of the CT scan and MRI is the inability to detect the ligamentum segment or nonpatent atretic arches. We recommend intraoperative bronchoscopy for all vascular ring patients. It confirms the presence or absence of tracheomalacia, bronchomalacia, complete tracheal rings, foreign bodies, and tracheal anomalies. These additional tracheal findings are important for surgical management and prognosis.

## SURGICAL APPROACHES

When patients develop clinical symptoms, surgical intervention is nearly always required, as medical treatment has no role in the treatment of these anomalies (see Fig. 84-25). Furthermore, unrepaired patients with vascular ring symptoms may develop severe upper respiratory infections and pneumonia requiring prolonged intubation. Adverse complications reported in unoperated patients include erosion of the esophagus into the tracheobronchial tree or aorta and aortic dissection.[26,27] The longer a symptomatic patient lives with an unoperated vascular ring, the more likely they will have a longer recovery related to more severe tracheobronchomalacia.

The more difficult situation is when the patient has a diagnosis of vascular ring made serendipitously when they have a scan for reasons unrelated to vascular ring symptoms. In these patients, careful, directed questioning may elicit symptoms that lead to a recommendation for surgery. In our experience all patients with a DAA and PAS have had symptoms and undergone repair. In contrast we have seen a number of patients with innominate artery compression

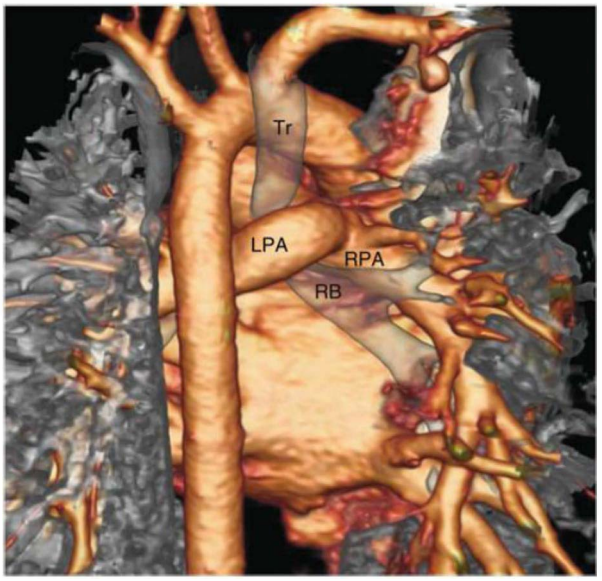



**FIGURE 84-15** Pulmonary artery sling. CTA Chest: 3D Reconstruction. The left pulmonary artery arises from the right pulmonary artery, courses over the right main bronchus, and then posterior to the trachea en route to the left lung. LPA, left pulmonary artery; RB, right mainstem bronchus; RPA, right pulmonary artery; Tr, trachea. (Courtesy of Cynthia Rigsby, MD, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL.)

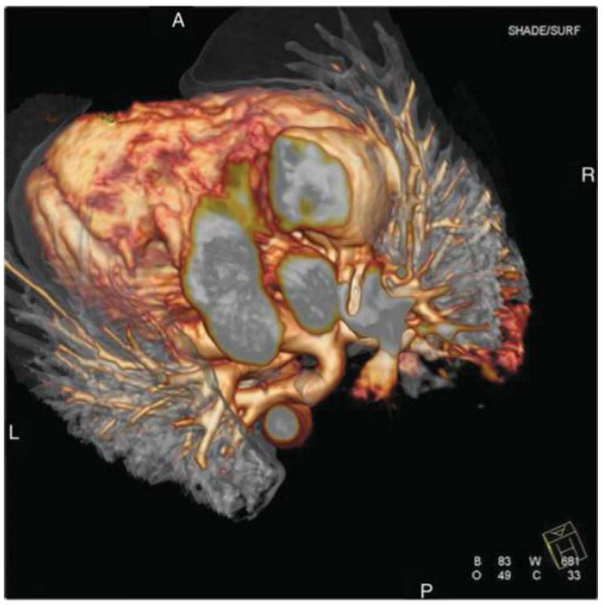



**FIGURE 84-16** Pulmonary artery sling. CTA Chest: 3D Reconstruction. This is a view from above in the same patient shown in Figure 84-15. The course of the left pulmonary artery to the left lung around the trachea is nicely demonstrated. (Courtesy of Cynthia Rigsby, MD, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL.)

syndrome and right arch and left ligamentum with no symptoms or very mild symptoms and we are carefully following them without an operation.

## SURGICAL PRINCIPLES

When approaching a patient with a vascular ring, several operative principles are used. First, we believe the preoperative CT scan is very important in determining the operative strategy, including the approach of either a left or right thoracotomy or midline sternotomy. Second, vascular clamps and fine prolene sutures are used to divide the vascular structures in order to avoid potential complications of crushing the vessel causing delayed hemorrhage. A third principle is that of not closing the pleura over the repair since adhesions in the area of the divided vascular ring can cause recurrent symptoms. Lastly, careful and adequate monitoring should be part of the routine, intraoperative practice. An arterial line is not usually required, but blood pressure cuff monitoring in upper and lower extremities is recommended. Pulse oximetry waveform on multiple extremities is a very helpful part of the monitoring process.

## DOUBLE AORTIC ARCH

The usual surgical approach for DAA repair is that of a thoracotomy opposite the location of the dominant aortic arch. For example, in a patient with a dominant right aortic arch (75 percent of patients), a left thoracotomy is the preferred approach and the smaller left arch is divided. In patients with a dominant left aortic arch, we prefer a right thoracotomy and the smaller right arch is divided. We would approach patients with balanced aortic arches and a left descending aorta through a left thoracotomy. In these particular patients we would recommend upper and lower extremity arterial line monitoring. A median sternotomy is used only when coexisting cardiac anomalies require repair.

The left thoracotomy is performed with a muscle-sparing technique through the fourth intercostal space. The lung is retracted anteriorly and the supreme intercostal vein is ligated and divided. The mediastinal pleura covering the aorta is incised superiorly and inferiorly while not extending anteriorly which may injure the vagus nerve, or posteriorly where the thoracic duct may be injured. The vascular ring is defined by first identifying the left subclavian artery and then determining the location of the posterior and anterior arches. The descending aorta is then dissected, but it may not be visible in situations where there is a right-sided descending aorta. In these cases the esophagus is prominently displayed. The ligamentum should also be identified. In the majority of cases, the left or anterior aortic arch is the smaller arch and is most commonly divided at the insertion to the descending aorta. In 34 percent of our cases, the left arch was atretic where it inserts into the descending aorta. This atretic area is an excellent site for arch division. Before dividing the

vascular structure, a test occlusion is performed to confirm no changes in the right or left upper extremity and carotid pulses. We then doubly clamp the arch between Potts ductus clamps, divide the arch, and the stumps are oversewn with two layers of running 5-0 or 6-0 polypropylene suture (Fig. 84-17A–C). In addition, the left ligamentum should also be divided. This prevents conversion of a DAA to a right aortic arch with left ligamentum. Once the arch is divided, any adhesive bands overlying the esophagus are divided. The left recurrent laryngeal nerve usually encircles the ligamentum arteriosum, and is carefully identified and avoided. The mediastinal pleura is left open to prevent adhesion formation. We do not routinely place chest tubes, but evacuate air in the thorax with a small suction catheter passed through the corner of the incision. Nearly all patients with a DAA can be extubated in the operating room and then admitted to the intensive care unit overnight. The next day the patient is usually transferred to the floor and they are often discharged home on the third day. In most patients the symptoms initially improve dramatically after surgery, but complete resolution of respiratory symptoms may take up to one year. It is helpful to inform parents of this preoperatively.

## RIGHT AORTIC ARCH WITH LEFT LIGAMENTUM

We approach these patients through a left thoracotomy. The only exception would involve associated cardiac anomalies that need simultaneous correction where median sternotomy is the preferred approach. In the unusual patient with situs inversus who has a left aortic arch with a right ligamentum;

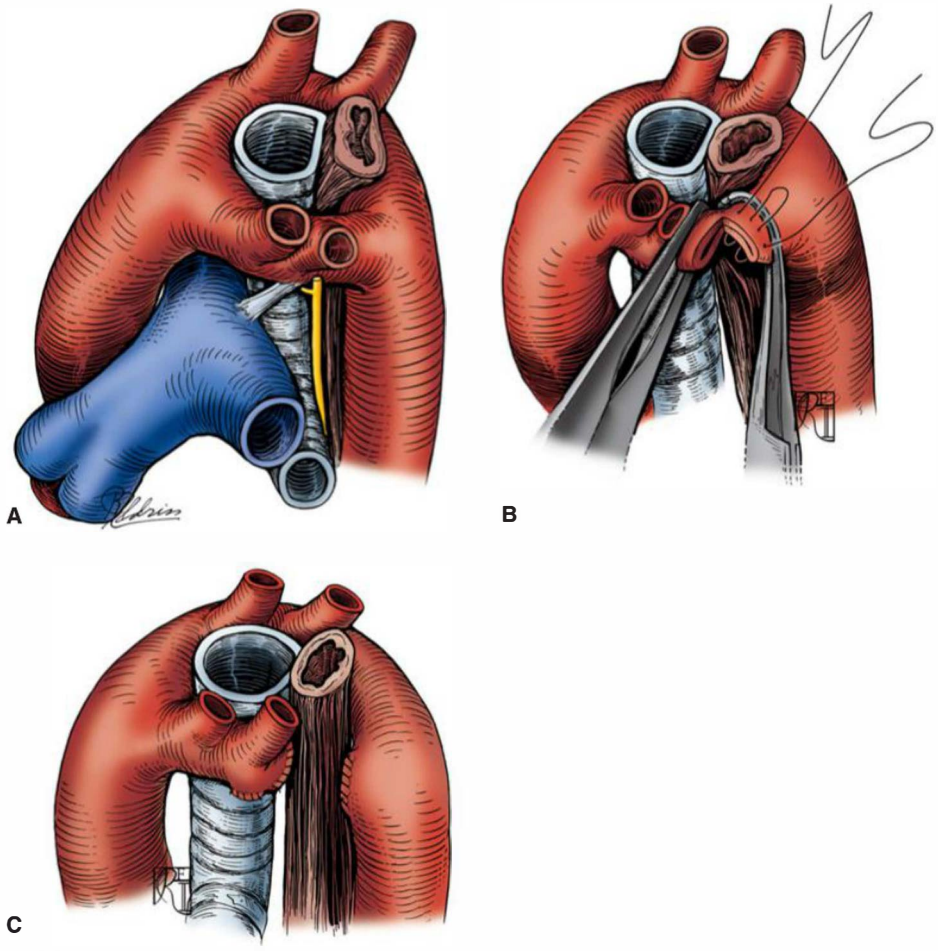



**FIGURE 84-17** Double aortic arch division. **A.** Double aortic arch, right arch dominant. The approach is via left thoracotomy. **B.** The left arch has been occluded proximally and distally with vascular clamps and partially divided. The stumps are oversewn with two layers of running Prolene suture. **C.** Left arch divided. The ligamentum has also been divided and oversewn. Ao, Aorta; L, left; LCCA, left carotid artery; RCCA, right carotid artery; LSA, left subclavian artery; RSA, right subclavian artery; PA, pulmonary artery; R, right. (Reprinted with permission from Backer CL, Mavroudis C. Vascular rings and pulmonary artery sling. In: Mavroudis C, Backer CL (eds). *Pediatric Cardiac Surgery*, 3rd ed. 2003:234–250.)

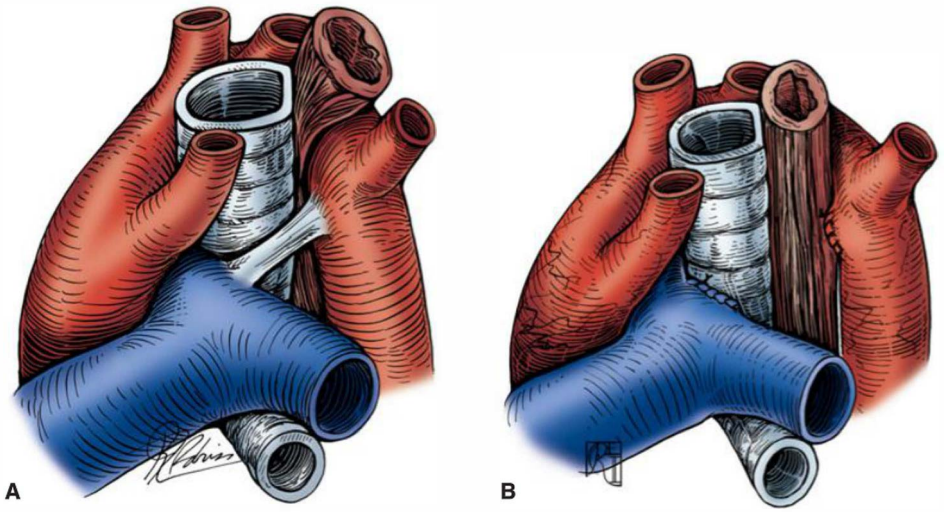



**FIGURE 84-18** Right aortic arch—division and oversewing of ligamentum arteriosum. **A.** Ligamentum completes the vascular ring. **B.** Ligamentum divided and oversewn. Ao, Aorta; LCCA, left common carotid artery; RCCA, right common carotid artery; LSA, left subclavian artery; RSA, right subclavian artery; MPA, main pulmonary artery. (Reprinted with permission from Backer CL, Mavroudis C. Vascular rings and pulmonary artery sling. In: Mavroudis C, Backer CL (eds). *Pediatric Cardiac Surgery* 3rd ed. 2003:234–250.)

a right thoracotomy is the preferred approach. The chest is entered with a muscle-sparing fourth intercostal space approach and the pleura covering the aorta is opened. The left subclavian artery arises from the descending aorta next to the origin of the ligamentum arteriosum in 66 percent of the cases. The ligamentum is dissected and doubly clamped with vascular clamps, divided, and the remnants are oversewn with running polypropylene suture (Fig. 84-18A and B). Because the ligamentum has no lumen, another surgical option is to doubly ligate with silk ties and reinforce with polypropylene sutures. The recurrent laryngeal nerve is carefully identified and preserved. Adhesive bands around the esophagus are divided and the pleura is left open. In patients with a preoperative diagnosis of right aortic arch and left ligamentum care must be taken to insure there is not a small atretic left arch connecting from anteriorly—an actual DAA. This can be a cause of residual symptoms after simple ligamentum division, and the atretic arch is not visible on CT or MRI.

An interesting subgroup of patients are those who present with the typical right aortic arch with left ligamentum but have aneurysmal dilation at the base of the retroesophageal left subclavian artery (Fig. 84-19). This is a Kommerell diverticulum which is the embryologic remnant of the left fourth arch.[16] With increasing growth of the aneurysm, the diverticulum may independently compress the esophagus and/or trachea. These patients often have had an initial surgical division of the ligamentum arteriosus but develop recurrence of their symptoms. Through the same left thoracotomy incision, the Kommerell diverticulum is excised, the base is oversewn, and the left subclavian artery is transferred to the left carotid artery (Figs. 84-20 and 84-21).[28] This procedure is also

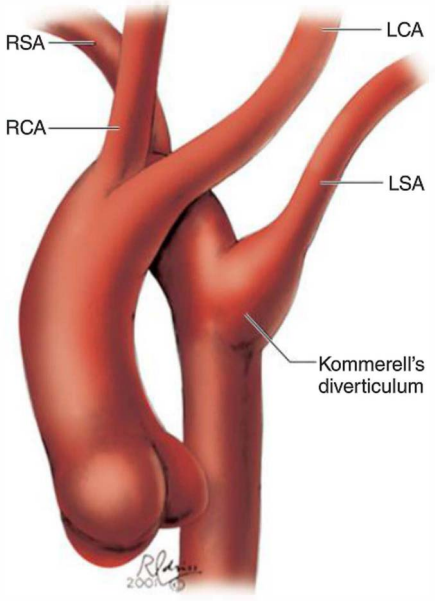



**FIGURE 84-19** Kommerell diverticulum. The origin of the left subclavian artery (LSA) in some patients with a right aortic arch is an aneurysmal embryologic remnant of the left fourth arch. This is called a Kommerell diverticulum. RCA, right carotid artery; RSA, right subclavian artery; LCA, left carotid artery. (Reprinted with permission from Backer CL, Hillman N, Mavroudis C, Holinger LD. Resection of Kommerell diverticulum and left subclavian artery transfer for recurrent symptoms after vascular ring division. *Eur J Cardiothorac Surg* 2002;22:64–69.)

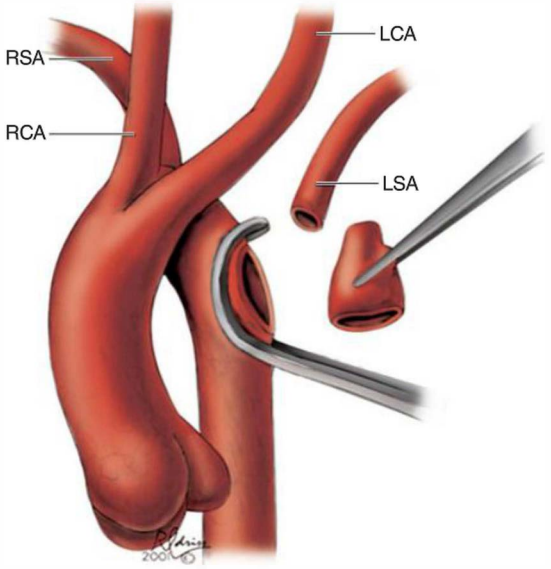



**FIGURE 84-20** Resection of a Kommerell diverticulum through a left thoracotomy. There is a vascular clamp partially occluding the descending thoracic aorta at the origin of the Kommerell diverticulum. The clamp on the left subclavian artery is not illustrated. The Kommerell diverticulum has been completed resected. RSA, right subclavian artery; LCA, left carotid artery; RCA, right carotid artery; LSA, left subclavian artery. (Reprinted with permission from Backer CL, Hillman N, Mavroudis C, Holinger LD. Resection of Kommerell diverticulum and left subclavian artery transfer for recurrent symptoms after vascular ring division. *Eur J Cardiothorac Surg* 2002;22:64–69.)

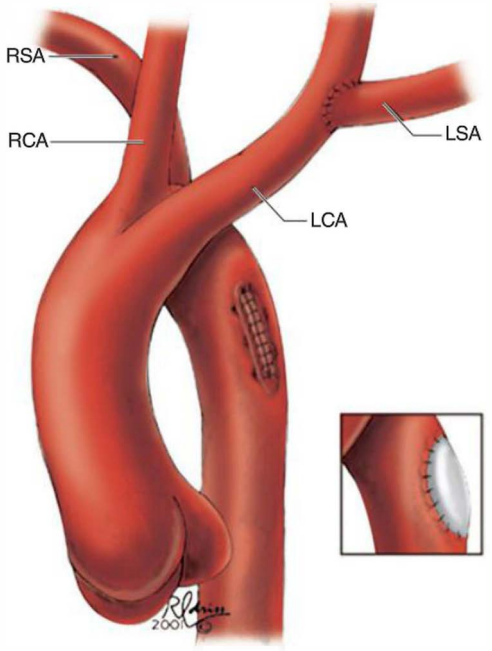



**FIGURE 84-21** Completed repair. The orifice at which the Kommerell diverticulum was resected is usually closed primarily. The orifice can also be patched with polytetrafluoroethylene if necessary (as shown in the inset). The left subclavian artery has been implanted into the side of the left common carotid artery with fine running polypropylene sutures. LCA, left carotid artery; RCA, right carotid artery; LSA, left subclavian artery; RSA, right subclavian artery. (Reprinted with permission from Backer CL, Hillman N, Mavroudis C, Holinger LD. Resection of Kommerell diverticulum and left subclavian artery transfer for recurrent symptoms after vascular ring division. *Eur J Cardiothorac Surg* 2002;22:64–69.)

preferred as a primary operation in the patients with a right arch, left ligamentum, and large Kommerell diverticulum.

## PULMONARY ARTERY SLING

A median sternotomy with cardiopulmonary bypass support is now the preferred approach for PAS repair.[29] Intraoperative bronchoscopy is critically important in determining the extent of tracheal compression and whether or not complete tracheal rings are present. If airway reconstruction is required, the intracardiac repair is performed first to avoid potential contamination from the tracheal reconstruction. Since 1985, we have used normothermic cardiopulmonary bypass with the heart beating for all PAS patients. The left PA is divided at its origin from the right PA. The right PA opening is closed primarily. The left PA is mobilized under the trachea and brought over to the left side of the mediastinum. It is then pulled anteriorly to the site on the main PA where the ligamentum has usually been divided. An opening is created in the main PA and the left PA is reimplanted at this site (Figs. 84-22 and 84-23). The patient is ventilated and weaned off cardiopulmonary bypass. If the airway requires repair the endotracheal tube is pulled up near the vocal chords. A tracheal resection is performed for a short segment stenosis (<6 rings) and a slide tracheoplasty is performed for long segment tracheal stenosis.[30] The reconstruction of the trachea follows general tracheal surgery principles which include extensive mobilization, preservation of the lateral blood vessels, and tension-free anastomosis. After reconstruction, the endotracheal tube is advanced beyond the site of an anastomosis which is externally marked with surgical clips that will help identify the reconstruction during the postoperative chest x-ray. For patients with unilateral agenesis of the right lung the PA sling can in some cases be repaired by translocation rather than reimplantation.[31,32]

## INNOMINATE ARTERY COMPRESSION

The repair of innominate artery compression syndrome is usually accomplished with suspension of the innominate artery to the sternum through a right anterior minithoracotomy. Through this limited incision, the right lobe of the thymus is excised. The pericardium is opened anterior to the phrenic nerve near the ascending aorta and the innominate artery. The aorta is pexed with three pledgetted permanent sutures, one at the junction of the ascending aorta with the innominate artery, a second on the proximal innominate artery, and a

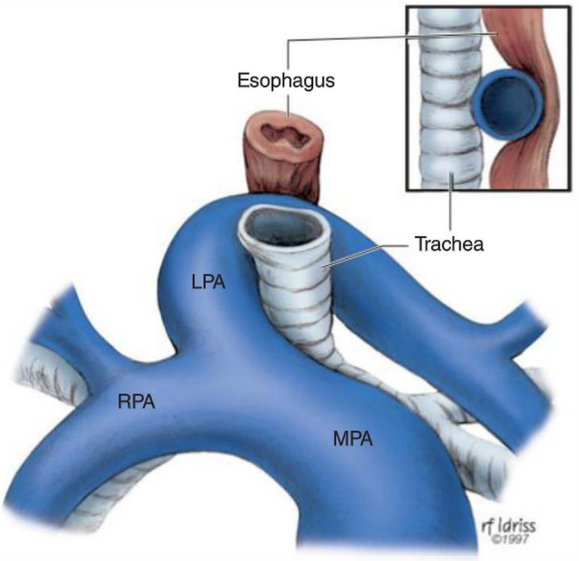



**FIGURE 84-22** Pulmonary artery sling. The left pulmonary artery (LPA) originates from the right pulmonary artery (RPA) and courses between the esophagus and trachea to reach the left lung. Inset: Lateral view shows anterior compression of the esophagus. MPA, main pulmonary artery. (Reprinted with permission from Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: Vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds). *Pearson's Thoracic and Esophageal Surgery.* Philadelphia: Churchill Livingstone Elsevier, 2008:242–255.)

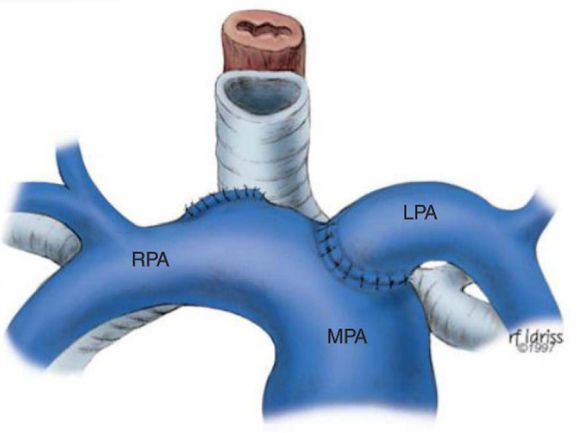



**FIGURE 84-23** Repaired pulmonary artery sling. The left pulmonary artery (LPA) has been implanted into the main pulmonary artery (MPA) anterior to the trachea. The origin of the LPA from the right pulmonary artery (RPA) has been oversewn with interrupted prolene suture. (Reprinted with permission from Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: Vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds). *Pearson's Thoracic and Esophageal Surgery.* Philadelphia: Churchill Livingstone Elsevier, 2008:242–255.)

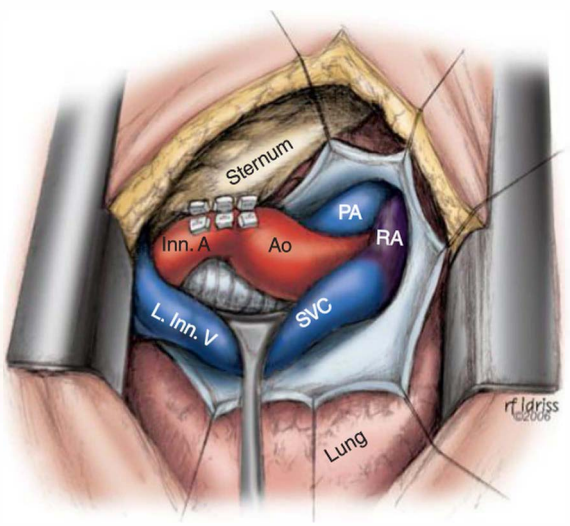



**FIGURE 84-24** Innominate arteriopexy. Through a right anterolateral thoracotomy the rigth lobe of the thymus is excised. The innominate artery is pexed to the posterior sternum with three pledgetted mattress sutures. (Ao, Aorta; Inn. A, Innominate artery; PA, Pulmonary artery; RA, Right atrium; SVC, Superior vena cava; L. Inn. V., left innominate vein.) (Reprinted with permission from Backer CL, Mavroudis C, Stewart RD, Holinger LD. Congenital anomalies: Vascular rings. In: Patterson GA, Cooper JD, Deslauriers J, Lerut AE, Luketich JD, Rice TW (eds). *Pearson's Thoracic and Esophageal Surgery.* Philadelphia: Churchill Livingstone Elsevier, 2008:242–255.)

third on the ascending aorta (Fig. 84-24). Careful monitoring of the right arm blood pressure and pulse oximetry will prevent stenosis of the right subclavian artery. In addition, guidance by intraoperative bronchoscopy determines the extent of tracheal traction required to relieve the compression.

## VIDEO-ASSISTED TECHNIQUE OF MANAGEMENT OF VASCULAR RING

At some centers, VATS has become the preferred operative approach for selected vascular ring patients.[33,34] After single lung ventilation, the patient is positioned in a right lateral decubitus position. Four thoracostomy working ports are inserted which will admit a camera (usually a 5-mm port), lung retractor, grasping forceps, and cautery probe. The optimal positioning of the ports is dependent on the surgeon's preference but the camera is typically placed at the tip of the scapula and the remaining ports are placed inferiorly and laterally to allow adequate movement of the working ports. Of note, the small child's thoracic cavity makes the relative motion of the instruments more crowded and limited than in an adult. After the lung is retracted, the remaining part of the operation proceeds in the usual fashion as for an open approach, except that clips are used to ligate the vascular ring before the division of the ring is performed. The essential principles of adequate exposure and definition of the vascular ring is critical when working through limited access. The

ideal candidate for this surgical approach is the child with an atretic arch (nonpatent) or a ligamentum. We have not used VATS in our practice, given the risk of catastrophic bleeding from a slipped clip with a patent arch. In addition, the morbidity of a muscle-sparing thoracotomy is quite small.

## TRACHEOBRONCHOMALACIA

A major morbidity intrinsic to many vascular ring patients is dynamic airway collapse due to lack of structural support, termed tracheobronchomalacia. Severe malacia is present in approximately 5 to 10 percent of vascular ring patients. This problem will cause the child to continue to have noisy respiratory symptoms after surgery. The key is to look for steady clinical improvement in the postoperative period and to remember that there is no definite time period for all the symptoms to disappear. However, if the noisy breathing symptoms fail to improve or get worse, then bronchoscopy should be repeated to secure the diagnosis of tracheal or bronchial malacia. The timing of the bronchoscopy is a clinical decision. Some guiding principles for when to perform the bronchoscopy: (1) if after extubation, the patient maintains excessive work of breathing with failure to grow, and

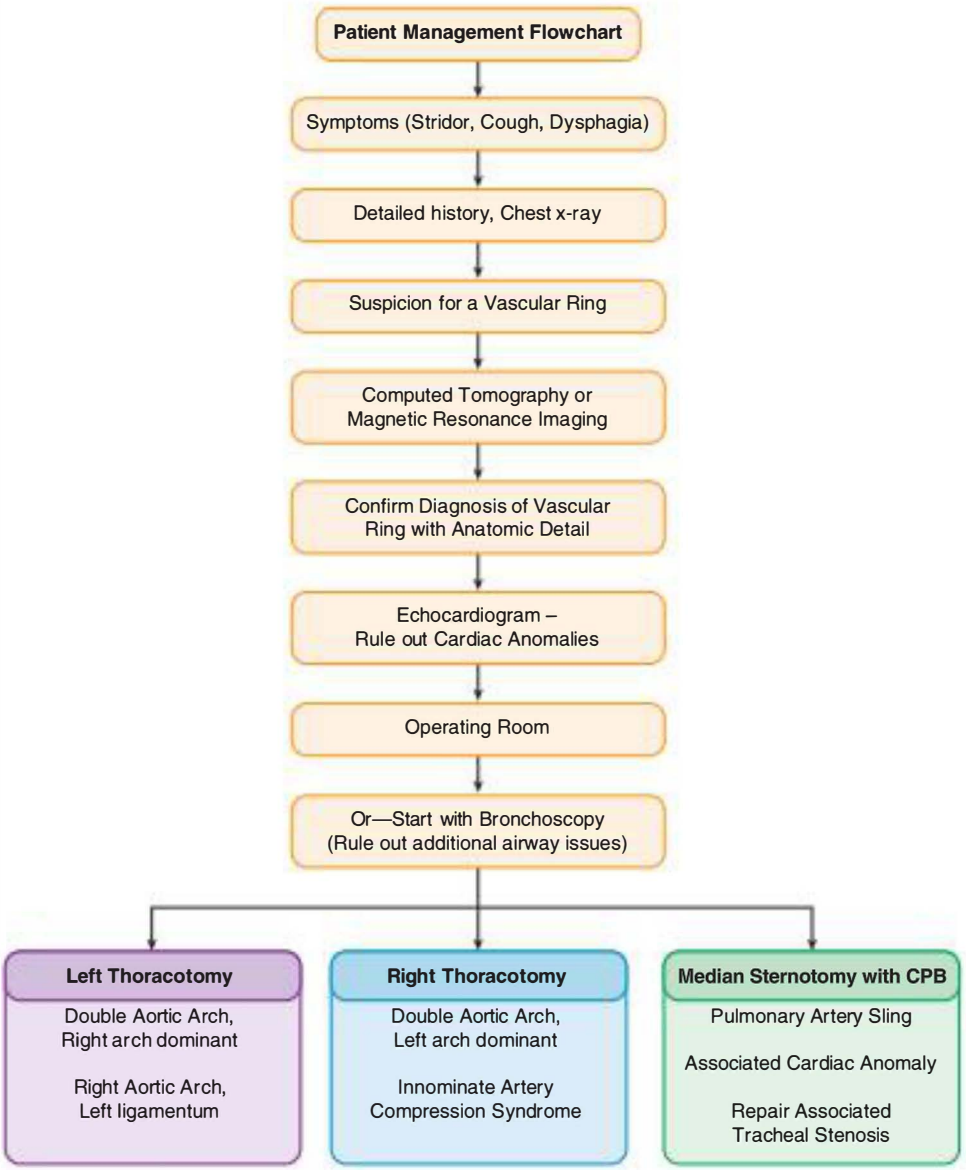



**FIGURE 84-25** Patient management flowchart.

(2) if the respiratory symptoms still persist with no improvement after 2 to 3 weeks postoperatively. A CT or MRI scan may provide additional or confirmatory anatomical detail of the trachea to determine whether a reoperation is warranted.

The management of tracheobronchomalacia appearing postoperatively is not straightforward, and varies from patient to patient. The first step in the management is to confirm with a CT scan that the vascular ring was successfully divided and no residual ring of tissue is present. Conservative management is the initial strategy, with surgical options including aortopexy, tracheostomy, external splinting, and internal stenting. We prefer aortopexy as a means of externally stenting the trachea, but in rare patients tracheostomy may be required to provide the necessary positive pressure support. Intramural stenting with thin-walled silicon stents or self-expandable metallic stents are additional options, although these stents are not ideal and have their own limitations, including mucus plugging, stent migration, and intrastent granulation tissue formation.[35] Furthermore, stents do not provide a permanent solution, as all stents need eventual removal. In summary, the management of tracheobronchomalacia is a rare but difficult postoperative morbidity that is usually treated conservatively.

## OUTCOMES

The overall outcome of patients with surgically treated vascular rings is extremely favorable. We reported our experience with 209 infants and children with vascular rings reported from 1946 to 2003.[11] No hospital deaths occurred after 1959. The primary preoperative study used for diagnosis has shifted from barium swallow to CT scan as the current practice. All patients in our practice undergo preoperative echocardiogram and pre- or intraoperative bronchoscopy. During this period, the mean hospital length of stay decreased to three days. Only four patients (2 percent) had persistent malacia that required aortopexy between 2 months and 4 years postoperatively. The results in patients with pulmonary sling are also quite good. We reported 16 patients operated on through a midline sternotomy using cardiopulmonary bypass in 1999.[29] No operative deaths were reported; however, one patient died from long term complications of tracheal surgery. We now have 34 patients who have undergone PAS repair using cardiopulmonary bypass and no operative mortality. Patients with vascular rings require a high index of suspicion to come to the diagnosis, but once the diagnosis is established, surgical repair can be accomplished with very low morbidity and essentially no mortality (Fig. 84-25).

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## VASCULAR RINGS AND PULMONARY ARTERY SLING BOARD REVIEW QUESTIONS (CHAPTER 84)

1. Which of the following is an incomplete ring?
   A. Double aortic arch, right dominant
   B. Right arch with retroesophageal left subclavian artery
   C. Right arch with mirror imaging branching
   D. Double aortic arch, left dominant
   E. Left arch with aberrant right subclavian artery

2. Which is correct regarding clinical presentation and diagnosis of vascular anomalies?
   A. Neonates usually present with esophageal compression.
   B. Patients with a double aortic arch present later in life.
   C. Pulmonary artery sling usually presents during the first year of life.
   D. The "four artery sign" is seen in innominate artery compression.
   E. MRI easily detects the ligamentous segment.

3. Which is correct regarding operative technique for vascular anomalies?
   A. The usual approach for double aortic arch repair is on the same side as the dominant arch.
   B. A balanced double arch and left descending aorta should be approached through a right thoracotomy.
   C. A left thoracotomy is preferred for the patient with situs inversus and a left arch with a right ligamentum.
   D. For repair of a Kommerell diverticulum and vascular ring, the left subclavian artery should be transferred to the left carotid artery.
   E. Circulatory arrest is the preferred strategy for pulmonary artery sling.

4. Which of the following would not be a suitable solution for a patient with tracheobronchial malacia?
   A. Internal stenting
   B. Aortopexy
   C. External splinting
   D. Tracheal resection
   E. Tracheostomy

5. Which of the following is true for outcomes after surgery for vascular anomalies?
   A. Mean length of stay is 5 days.
   B. Surgery for tracheobronchial malacia is required in 5 to 10 percent of patients.
   C. Mortality for repair of pulmonary artery sling is zero.
   D. 10 to 20 percent of patients with vascular rings have severe tracheobronchial malacia.
   E. Video-assisted techniques are ideally suited for the patient with a double aortic arch.

## ANSWERS

1. **Answer: E.** A left aortic arch with an aberrant right subclavian artery does not form a complete vascular ring. Double aortic arch forms a complete vascular ring, as does a right arch with a ligamentum arteriosum.
2. **Answer: C.** Pulmonary artery sling usually presents during the first year of life. Neonates usually present with tracheal compression. Patients with double aortic arch usually present early in life and the "four artery sign" on CT is typical. MRI is unable to detect the ligamentous segment or nonpatent atretic arches.
3. **Answer: D.** A Kommerell diverticulum and vascular ring is repaired by translocating the left subclavian artery to the left carotid artery. The usual approach for a double aortic arch is on the opposite side from the dominant arch. A balanced double arch and left descending aorta should be approached through a left thoracotomy. A right thoracotomy is preferred for the patient with situs inversus and a left arch with a right ligamentum. Circulatory arrest is typically not required for repair of pulmonary artery sling.
4. **Answer: D.** Aortopexy, internal stenting, external splinting, and tracheostomy are all suitable options for the treatment of a patient with tracheobronchial malacia that is resistant to conservative therapy. Tracheal resection is not indicated.
5. **Answer: C.** Current surgical mortality for repair of pulmonary artery sling is zero. Mean length of stay is approximately 3 days, and surgery for tracheobronchial malacia is required in less than 5 percent of patients. Severe tracheobronchial malacia is present in 5 to 10 percent of vascular ring patients. Video-assisted techniques are best reserved for patients with nonpatent/atretic archs or ligamenta.

85

# Ebstein's Anomaly

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## KEY CONCEPTS

- Epidemiology
  - Ebstein's anomaly occurs in 1 percent of all congenital heart defects and represents 0.3 to 0.8 percent of all cardiac malformations diagnosed during the first year of life.
- Pathophysiology
  - The degree of displacement and morphology of the tricuspid leaflets determine the degree of regurgitation. The attachments of the anterior leaflet to the right ventricular outflow tract may inhibit normal flow to the pulmonary artery, thus creating various degrees of outflow tract obstruction or functional/anatomical pulmonary atresia with duct-dependent pulmonary circulation. Diminishing forward output, with increasing backflow to the right atrium, leads to severe cyanosis due to right-to-left shunting at the atrial level. Right ventricular dilation can induce leftward bulging of the interventricular septum, thus compromising left ventricular function. Progressive cardiomegaly can affect the growth of the lungs, inducing lung hypoplasia.
- Clinical features
  - Clinical presentation can occur at any age. Newborns will often manifest cyanosis and congestive heart failure, accompanied by circulatory collapse. After infancy, the child may show limited cyanosis during exercise. With increasing age arrhythmias, cyanosis and limited exercise tolerance (with dyspnea and palpitations) become more prominent. Mild forms may not be symptomatic until adulthood.
- Diagnostics
  - Echocardiography is diagnostic. Cardiac catheterization is not routinely performed, unless the pulmonary artery pressure and vascular resistance require evaluation.
- Treatment
  - In neonates and young infants, the indications for surgery are ventilator dependence, severe cardiac failure, and severe tricuspid insufficiency with prostaglandin-dependent circulation.
  - In older patients, surgery is indicated due to symptoms of poor growth, decreased exercise tolerance, cyanosis, progressive cardiomegaly (cardiothoracic ratio >0.6), reduced left ventricular function, tachyarrhythmias, and the presence of significant associated lesions. Timely operation is warranted before cardiomegaly develops and the functional status deteriorates.
  - Surgical therapy should restore tricuspid valve competence and address the inadequacy of the inefficient right ventricle. In children, tricuspid valve plasty with biventricular correction should take preference over tricuspid valve replacement or single ventricle pathway. Surgical repair consists of (1) reconstruction of the tricuspid valve, (2) consideration of plication or resection of the atrialized right ventricle, (3) closure of the atrial communication and correction of any associated anomalies, (4) arrhythmia surgery, and (5) right reduction atrioplasty. In special situations, the concept of one and one-half ventricular repair or of the single ventricular pathway should be adopted.
- Outcomes/prognosis
  - With current surgical techniques, repair is feasible in the vast majority of patients and results in low early mortality (<5 percent); reintervention rate and survival is of >80 percent at 20 years. Newborns and small infants remain, however, still a challenge.

## INTRODUCTION

Ebstein's anomaly is a rare congenital heart malformation of the right ventricle and tricuspid valve. Failure of delamination of the tricuspid valve, especially of the posterior and septal leaflets from the underlying myocardium, results in variable degree of tricuspid valve and right ventricular deformity as first described by Wilhelm Ebstein,[1] a German pathologist.

The natural history of this malformation is influenced by a high rate of intrauterine and neonatal death, especially when the anomaly is associated with severe deformity of the tricuspid valve and cyanosis. At the other end of the spectrum, patients with mild dysfunction of the tricuspid valve may remain asymptomatic until late adult life.[2,3] Management, therefore, often requires a choice between a conservative approach and operative intervention. Currently available surgical techniques have demonstrated survival and functional benefit even for those patients in whom the malformation is severe.[4–7]

## DEFINITION AND MORPHOLOGICAL FEATURES

Ebstein's anomaly occurs relatively late in heart development, as the inner surfaces of the right atrium and ventricle are undermined distal to the atrioventricular sulcus. The anterior leaflet is formed earlier than the posterior and septal leaflets, during the third and fourth month of gestation, which may explain the differences in maturation.

The anomaly is characterized by the following (Fig. 85-1):

1. Tricuspid valve malformations
   a. The septal and posterior leaflets are displaced toward the apex of the right ventricle with a variable degree of adherence to the myocardium (spiral failure of delamination).
   b. The sail-like, redundant anterior leaflet has a normal attachment to the tricuspid valve annulus, but is frequently fenestrated, having chordal attachments to the ventricular wall and eventually also linear attachments (fibrous and muscular attachments) between the leaflet and the myocardium.
2. The right ventricle is malformed and consists of
   a. A thin-walled "atrialized" component, defined as a segment of the right ventricle, from the level of the "true" tricuspid annulus to the level of displacement of the septal and posterior leaflets;
   b. A thick-walled functional component ("true right ventricle cavity"), consisting of apical and outlet portions, often obstructed by chordal attachments of the anterior leaflet of the tricuspid valve. The inlet portion is small or nonexistent. The cavity of the functional right ventricle is usually smaller and, histologically contains fewer myocytes and more fibrous tissue than a normal right ventricle.

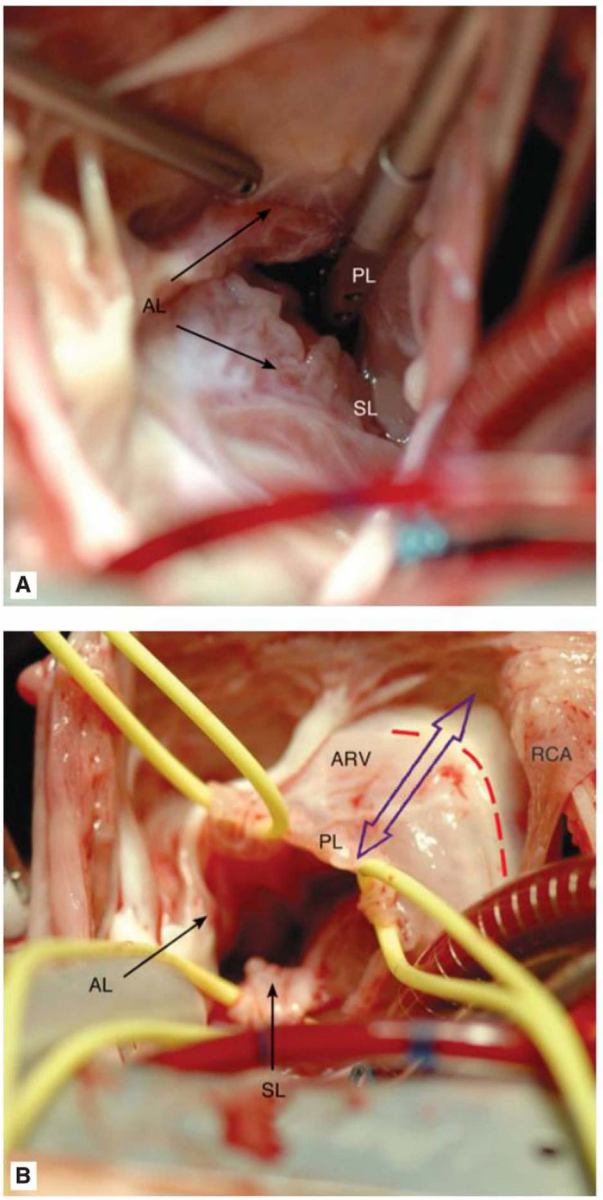



**FIGURE 85-1** Ebstein's anomaly in a 6-month-old patient. **A.** Note the severe displacement of the posterior and septal leaflets. **B.** Vessel loops surround the fibrous and muscular attachments of the leading edges of the leaflet to the underlying myocardium. Note the atrialized portion of the right ventricle and position of the right coronary artery. RCA, right coronary artery; AL, anterior leaflet; PL, posterior leaflet; SL, septal leaflet; ARV, atrialized right ventricle.

The most commonly associated anomaly is an atrial septal defect or persistent foramen ovale (in about 90 percent of the cases). Survival in symptomatic newborns with severe obstruction to pulmonary outflow depends on the presence of a patent ductus arteriosus in addition to atrial-level communication. The Wolff–Parkinson–White syndrome is

present in about 10 percent of the cases. Association with an atrioventricular septal defect, ventricular septal defect, tetralogy of Fallot, congenitally corrected transposition of the great arteries, aortic coarctation or other defects is rarely observed.

## ETIOLOGY

The majority of cases of Ebstein's anomaly are sporadic, but familial cases have been reported. Gestational exposure to lithium increases the relative risk of any malformation, including cardiac anomalies, by two to three times.

## PATHOPHYSIOLOGY

### Tricuspid Valve

The degree of displacement, hypoplasia, and tethering of the leaflets, as well as existing fenestrations and the dilation of the right atrioventricular junction, determine the degree of regurgitation. The large anterior leaflet with the linear attachments may divide the inlet from the muscular portion, mimicking tricuspid stenosis or even tricuspid atresia if there are no leaflet fenestrations. Attachments of the anterior leaflet to the right ventricular outflow tract can also inhibit the normal flow to the pulmonary artery, inducing the development of pulmonary atresia in about 10 percent of infants.

### Right Ventricle

The two parts of the right ventricle show a specific movement pattern affecting forward flow. During atrial systole, the atrialized component balloons out, which may significantly reduce forward flow into the functional component of the right ventricle. During ventricular systole, the atrialized component of the right ventricle contracts, pushing the blood backward to the right atrium, resulting in an increase in systemic venous pressure and subsequent right atrial dilatation, even in the absence of significant tricuspid valve regurgitation.

### Left Ventricle

Right ventricular dilation can induce the interventricular septum to bulge toward the left and thus significantly compromise left ventricular function (ventricular interdependence).

### Postnatal Hemodynamics

Depending on the severity of Ebstein's anomaly and the associated heart defects, postnatal hemodynamics can be extremely variable.

#### MILD DISPLACEMENT OF THE TRICUSPID VALVE

With mild displacement of the posterior and septal leaflets of the tricuspid valve and good function of the right ventricle, postnatal circulation will be normal, with only mild tricuspid regurgitation and sufficient antegrade pulmonary blood flow.

#### MODERATE DISPLACEMENT OF THE TRICUSPID VALVE

A higher degree of displacement results in a higher grade of tricuspid regurgitation, enhanced by the postnatally high pulmonary vascular resistance. Elevated right atrial pressure promotes right-to-left shunting on an atrial level with a variable degree of cyanosis, depending on the ductal flow. If the pulmonary outflow tract is patent, ductal flow increases the right ventricle afterload and has a negative impact on tricuspid valve function. Clinically tolerable closure of the duct with sufficient antegrade pulmonary blood flow is a positive prognostic factor in infants.[8] In the case of pulmonary atresia, the duct may be the only source of pulmonary blood flow.

#### SEVERE DISPLACEMENT OF THE TRICUSPID VALVE

Severe displacement of the posterior and septal leaflets results in severe tricuspid regurgitation and a large atrialized component of the right ventricle. If the duct is open, the right ventricle is usually not capable of opening the pulmonary valve, mimicking pulmonary atresia. Systemic venous return is shunted to the left ventricle across the atrial septal defect, and the resulting physiology is similar to that of tricuspid or pulmonary atresia.

### Hemodynamics Beyond Infancy

Children with minor tricuspid regurgitation and a functioning right ventricle come to clinical attention because of associated lesions. Volume overload of the right ventricle, due to a left-to-right shunt at the atrial level, might accelerate the development of important tricuspid regurgitation. With more prominent tricuspid regurgitation, cyanosis may occur on exertion, unmasking the limited capability to augment right ventricular output.

### Arrhythmias

Arrhythmias occur in 20 to 30 percent of all patients. Deficient fibrous development of the tricuspid valve annulus, with accessory muscular pathways across the atrioventricular junction, results in a high incidence of preexcitation (Wolf–Parkinson–White syndrome). A stretched, fibrotic and dysplastic right ventricular myocardium is a substrate for ventricular arrhythmias. Incomplete fibrous encasement

of the atrioventricular node and the bundle of His can cause reentry tachycardias. Rapid conduction of atrial arrhythmias or ventricular tachycardias accounts for 3 to 10 percent of sudden death.

## CLINICAL FEATURES

Patients may present at any age. Prenatally, the fetus may suffer from tachyarrhythmia, pulmonary parenchymal hypoplasia secondary to cardiomegaly, or hydrops. Newborns and young infants often present with cyanosis, tachypnea, enlarged liver, and other symptoms of cardiac failure. Neonates disclosing the most extreme forms of this anomaly will become critically ill immediately after birth, requiring intensive medical treatment and ventilatory support. Beyond infancy, the child may show limited cyanosis during exercise, but there is rarely failure to grow and development of congestive heart failure with cardiomegaly. With increasing age, cyanosis and limited exercise tolerance, with dyspnea and palpitations, will become more prominent. The dominant mode of clinical presentation in adolescents and young adults is arrhythmia and limited exercise tolerance. Mild forms of Ebstein's anomaly may not become symptomatic until adulthood.[3]

## DIAGNOSTIC MODALITIES

### Physical Examination

Prominence or asymmetry of the chest is linked to the dilated right heart. Cyanosis and digital clubbing are secondary to a chronic right-to-left shunt. Multiple abnormal sounds and murmurs are evident on cardiac auscultation. The first and the second heart sounds are widely split due to increased excursion of the anterosuperior leaflet, the delayed closure of the abnormal tricuspid valve, and the late closure of the pulmonary valve secondary to right bundle branch block. A systolic murmur usually suggests either some associated cardiac anomaly or tricuspid regurgitation.

#### CHEST X-RAY

Variable cardiomegaly, secondary to enlargement of the right atrium, is typical. Pulmonary vascular markings are normal or diminished, according to the degree of right ventricular outflow tract obstruction (Fig. 85-2).

#### ELECTROCARDIOGRAM

Characteristically, the ECG is abnormal, presenting with a right bundle branch block and prominent P-waves that reflect the enlargement of the right atrium. The P-R interval may be prolonged up to a first degree of AV block, and the occurrence of the Wolff-Parkinson-White syndrome is not infrequent. Atrial rhythm problems such as atrial fibrillation, atrioventricular nodal reentry tachycardia, focal atrial tachycardia, and atrial flutter are common in older patients. Holter monitoring should therefore be performed repeatedly, especially in the symptomatic patient.

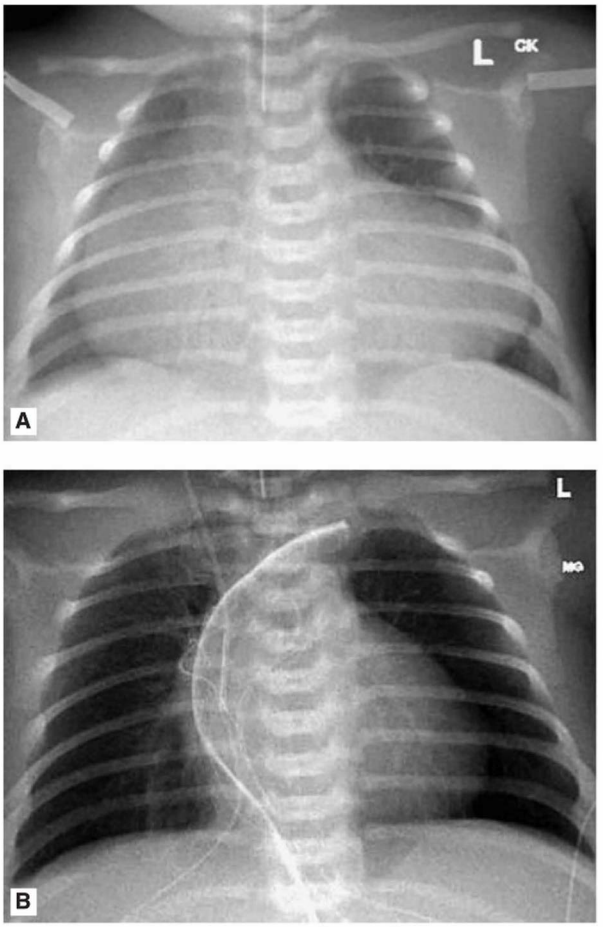



**FIGURE 85-2** Ebstein's anomaly. Chest x-ray of newborn before (**A**) and after corrective surgery (**B**).

#### ECHOCARDIOGRAPHY

Echocardiography is diagnostic, not only for outlining the morphology and physiology, but also for assessing the suitability for reconstructive surgery (Fig. 85-3). The evaluation should clarify:

1. The morphology of the tricuspid valve
   a. Displacement of the annular hingepoint of the septal and posterior leaflets
   b. Morphology of the anterior leaflet with elongation, tethering, chordal support, and mobility of the free leading edge
   c. Papillary muscle location and attachments

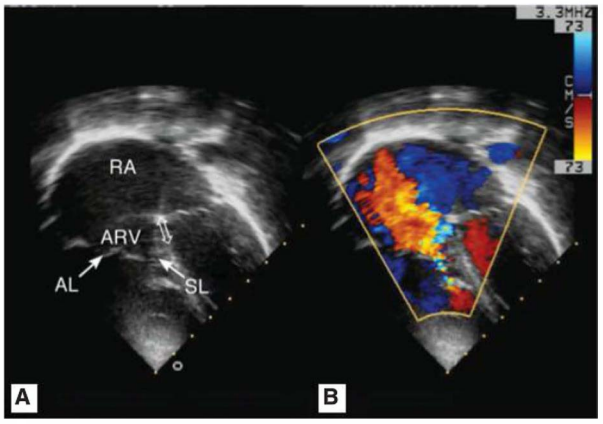



**FIGURE 85-3** Ebstein's anomaly. **A.** Echocardiography shows the displacement of the septal leaflet, the size and position of the anterior leaflet of the tricuspid valve. **B.** The Doppler echocardiogram shows moderate tricuspid regurgitation. RA, the right atrium; ARV, atrialized right ventricle; AL, anterior leaflet; SL, septal leaflet.

2. Function of the tricuspid valve
   a. Degree of regurgitation based on Doppler scanning of jet velocity and not on the quantity of regurgitation
   b. Number of regurgitant jets
   c. Function and mobility of the anterior, septal and posterior leaflets
3. The right ventricle
   a. Size and function
   b. Morphology of the outflow tract
      i. Degree of obstruction by the anterior leaflet
      ii. Function and morphology of the pulmonary valve
4. The left ventricle
   a. Systolic and diastolic function
   b. Presence of noncompaction
5. The size of the PDA, atrial septal defect, and shunt direction
6. Associated anomalies

Echocardiographic evaluation has several pitfalls: The severity of tricuspid regurgitation is frequently underestimated; therefore, surgical intervention might be inappropriately deferred. Proper evaluation of the right ventricular outflow tract, the proximity of the tricuspid valve tissue to the pulmonary valve (indicating severe displacement of the leaflet) and assessment of the effective capacity of the right ventricle below the point of coaptation are challenging.[9]

### MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging complements echocardiography in delineating apical displacement, mobility and function of the tricuspid valve. This modality is accurate in evaluating the size and the function of the atria, both ventricles and ventricular outflow tracts.

### EXERCISE TESTING

Exercise testing is used routinely to evaluate the patient before and after surgery, and aids in indicating the timing of surgical intervention.

### CATHETERIZATION

Diagnostic cardiac catheterization is not routinely performed, unless the pulmonary vascular resistance is to be evaluated before a planned bidirectional Glenn superior cavo-pulmonary anastomosis. A selective coronary angiogram is indicated in patients over 40 years of age or in those with a high risk of coronary artery disease. A preoperative invasive electrophysiological study with ablation is performed in patients with evidence of ventricular pre-excitation on ECG and in all patients with a history of recurrent supraventricular tachycardia, undefined wide-complex tachycardia, or syncope.[10]

## MEDICAL THERAPY

The main goal is to support newborns through the period of transition from fetal to neonatal circulation. All measures are therefore taken to lower pulmonary vascular resistance while preserving duct-dependent pulmonary circulation. The critically ill neonate requires mechanical ventilation, sedation, paralysis, hyperventilation, correction of metabolic acidosis, appropriate inotropic/volume management, and a prostaglandin $E_1$ infusion. After stabilization, when pulmonary vascular resistance begins to fall, the prostaglandin is stopped to allow ductal constriction. Subsequently, the true functional capability of the right ventricle in providing antegrade flow is evaluated. At this point, pulmonary vasodilator therapy may be useful.[11]

Older patients require either no treatment or treatment for symptoms of cardiac failure or arrhythmias. Oral anticoagulation should be considered in the case of paroxysmal or chronic atrial fibrillation or flutter.

## SURGICAL THERAPY

### Indication for Surgery

#### NEOANATES AND YOUNG INFANTS

Typically, the indications for surgery are ventilator dependence, severe cardiac failure, prostaglandin-dependent circulation, and gross cardiomegaly.[12]

#### OLDER CHILDREN AND ADULTS

Indications for operation include one or more of the following: poor growth, symptoms of dyspnea or decreased exercise tolerance (NYHA functional class III, IV), cyanosis (oxygen saturation <90 percent), paradoxical embolism, progressive cardiomegaly (cardiothoracic ratio >0.6), reduced left

ventricle function, tachyarrhythmias that are not controllable by medication or amenable to catheter-based intervention, and significant associated lesions (atrial septal defect, ventricular septal defects, pulmonary stenosis).[5,13,14] In asymptomatic patients, the indication for surgery remains controversial. The arguments in favor of earlier operation are[2]:

1. The natural history of patients who do not undergo operation is poor.
2. The surgical mortality of patients with late-stage complications is high.

A timely operation is therefore warranted before cardiomegaly develops and the functional status deteriorates. Currently, the operation can be considered in asymptomatic patients with low normal exercise tolerance, no right-to-left shunting, and only mild cardiomegaly (cardiothoracic ratio ≤0.6).[4,6] In children with mild symptoms but with significant enlargement of the right atrium due to massive tricuspid insufficiency, the risk of early rhythm disturbances is so high that surgery should be considered.[5]

# SURGICAL TECHNIQUES

## General Principles

Surgical therapy for Ebstein's anomaly should restore tricuspid valve competence and address the inadequacy of the inefficient RV. Especially in children, tricuspid valvuloplasty with biventricular correction should take preference over tricuspid valve replacement or a single ventricle pathway. Surgical repair consists of (a) reconstruction of the tricuspid valve, (b) consideration of plication or resection of the atrialized right ventricle (especially when it is thin-walled and moves paradoxically), (c) closure of the atrial communication and correction of any associated anomalies, (d) surgery for arrhythmia, and (e) right reduction atrioplasty. In special situations, the concept of one and one-half ventricular repair or of a single ventricular pathway should be considered. Heart transplantation is the last resort therapy. Reconstructive surgery is based either on the principle of anatomical repair[4,15,16] or monoleaflet repair.[13,17–19]

# ANATOMICAL REPAIR—CONE RECONSTRUCTION

## Principle

The cone reconstruction moves the new tricuspid valve orifice to the level of the true valve annulus, restoring the normal anatomical location of the tricuspid valve.[4,20]

## Advantages

The cone reconstruction restores the appearance of the normal tricuspid valve anatomy and its function, resulting in central diastolic blood flow and full coaptation of the leaflets. The normalization of the right ventricular volume and morphology is achieved by longitudinal plication of the atrialized right ventricle.

## Disadvantages

This technique raises concerns about tricuspid valve stenosis. However, the inclusion of the septal leaflet and the rotation of the cordless posterior leaflet tissue to enlarge the "cone" might minimize the risk of inflow obstruction.

## Technical Considerations

The important operative steps are as follows:

### "CORRECTION" OF FAILURE OF DELAMINATION

The anterior and posterior tricuspid valve leaflets are detached from the hingepoint. In a single piece, they are mobilized from their anomalous attachments in the right ventricle. The most important aspect of this surgical delamination is to incise all fibrous and muscular attachments between the body of the leaflet and the right ventricular myocardium, but to maintain all fibrous, or occasionally muscular, attachments of the leading edge of the leaflet to the underlying myocardium intact (Fig. 85-4). When a linear attachment is present, it is treated by making fenestrations in the distal aspect of the leaflet, thus creating the equivalent of "neochordae." Only the normal attachments of the anterior leaflet to the true tricuspid annulus and the proper subvalvular apparatus are left in place.

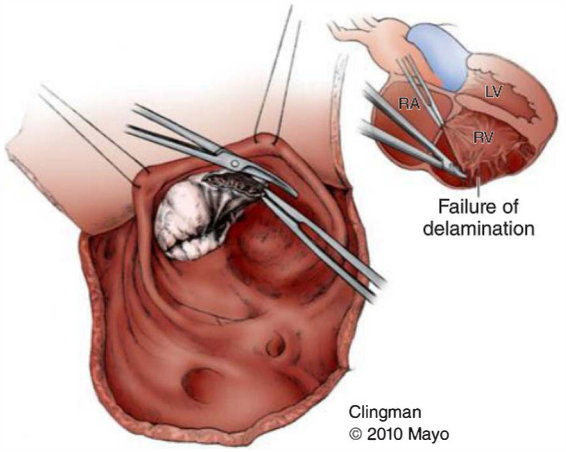



**FIGURE 85-4** Ebstein's anomaly and cone reconstruction. Detachment of the anterior leaflet and correction of failure of delamination. LV, left ventricle; RA, right atrium; RV, right ventricle. (Copyright and used with permission of Mayo Foundation for Medical Education and Research. All rights reserved)

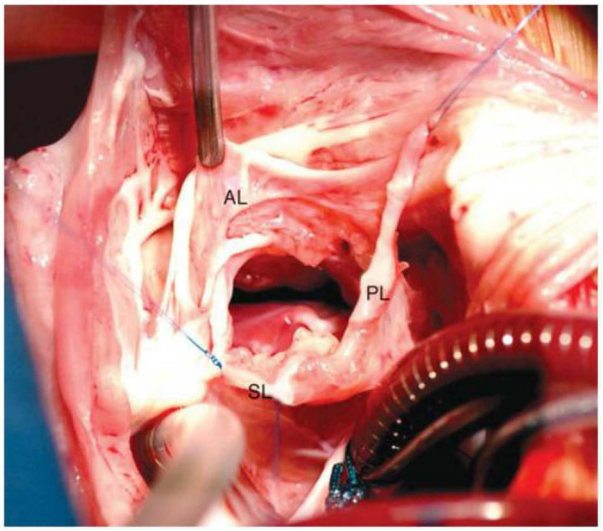



**FIGURE 85-5** Ebstein's anomaly and cone reconstruction in a 6-month-old patient. All fibrous and muscular attachments between the body of the leaflets and the right ventricular myocardium were incised. The cone reconstruction was completed by rotating the posterior leaflet clockwise to meet the proximal edge of the septal leaflet. AL, anterior leaflet; PL, posterior leaflet; SL, septal leaflet.

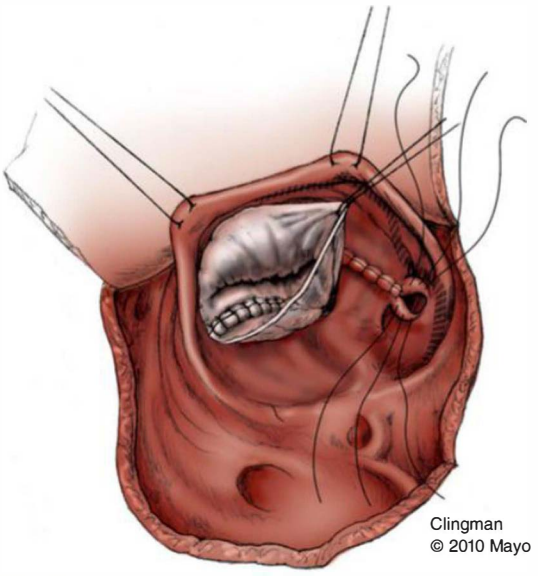



**FIGURE 85-6** Ebstein's anomaly and cone reconstruction. The suture line is advanced toward the atrioventricular groove, excluding the atrialized right ventricle. (Copyright and used with permission of Mayo Foundation for Medical Education and Research. All rights reserved)

## CREATING A CONE

The free edge of this valve complex is rotated clockwise for suture to the septal border of the anterior leaflet, thus creating a cone, the vertex of which remains fixed to the right ventricular apex. Additionally, the septal leaflet is extensively mobilized, in order to be incorporated into the cone wall wherever possible. Alternatively, fresh autologous pericardium is used to reconstruct the septal portion of the tricuspid valve.[16] This results in 360° of leaflet tissue that will make up the new tricuspid valve orifice (Fig. 85-5).

## EXCLUSION OF THE ATRIALIZED RIGHT VENTRICLE

The atrialized part of the right ventricle is then longitudinally plicated to exclude its thin part. Care is taken not to compromise the acute marginal branches of the right coronary artery (Fig. 85-6). Alternatively, the atrialized ventricular wall is excised longitudinally, restoring the right ventricular geometry.[16]

## ATTACHMENT OF THE TRICUSPID VALVE TO THE ANNULUS

The new valvular annulus is constructed (at the anatomically correct level) by means of plication of the true tricuspid annulus to match the proximal circumference of the cone-shaped valve. The base of the cone is sutured to the new valve annulus. The suture line is diverted slightly cephalad to the membranous septum and atrioventricular node to avoid heart block (Fig. 85-7).

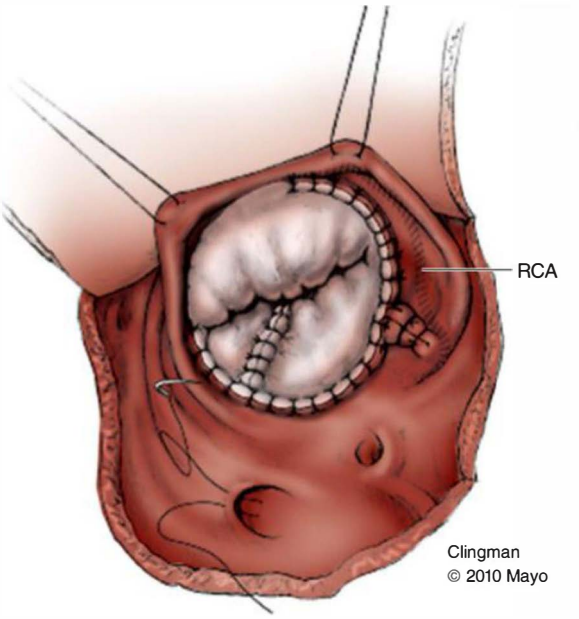



**FIGURE 85-7** Ebstein's anomaly and cone reconstruction. The base of the cone is sutured to the new valve annulus while the annulus is plicated. RCA, right coronary artery. (Copyright and used with permission of Mayo Foundation for Medical Education and Research. All rights reserved)

Additionally, the atrial septal defect is closed as a flap valve. The redundant right atrium is excised from each side of the atriotomy and then the atriotomy is closed.

## MONOLEAFLET REPAIR

### Principle

The repair is based on the use of the enlarged anterior leaflet, constructing a competent monoleaflet valve even though no usable septal or posterior leaflet tissue is present. The free leading edge of the anterior leaflet and at least 50 percent delamination of the anterior leaflet are required for successful reconstruction.[13]

### Advantages

If properly indicated and executed, the long-term functional outcome of the monolealfet valve is promising.

### Disadvantages

This type of reconstruction of the tricuspid valve generates an off-center diastolic blood flow.

## MONOLEAFLET APPROACH WITH TRANSVERSE PLICATION OF THE ATRIALIZED RIGHT VENTRICLE: DANIELSON TECHNIQUE[17]

### Technical Considerations

Transverse plication of the atrialized portion of the right ventricle brings the displaced valvular plane (posterior and septal leaflets) to the level of the "true" valvular plane. Because the spacing between each pledgetted mattress suture is wider at the annulus than at the valvular plane, the annulus is effectively downsized. The annulus may be further narrowed by plicating the free wall portion of the annulus to the septal portion. To improve the closing mechanism a posterior annuloplasty is added.

### Advantages

Internal transverse (apex to base) plication elevates the papillary muscle (thus facilitating the closure of the anterior leaflet against the septum in systole), obliterates the noncontractile portions of the atrialized right ventricle, and reduces the size of the annulus.

### Disadvantages

Transverse plication does not improve the volume and geometry of the right ventricle. There is a risk of myocardial ischemia and impairment of the right ventricular function due to torsion of the right coronary artery.

## MONOLEAFLET APPROACH WITH LONGITUDINAL PLICATION OF THE ATRIALIZED RIGHT VENTRICLE: CARPENTIER TECHNIQUE[18]

### Technical Considerations

The anterior leaflet is partially detached and the atrialized portion of the right ventricle is longitudinally plicated. After plication of the annulus, the anterior leaflet is partially rotated to reach the septal tricuspid region and is sutured to the anatomically correct level. In adult patients, the tricuspid annulus is remodeled and reinforced with a prosthetic ring.

### Advantages

Longitudinal plication of the atrialized right ventricle and attachment of the anterior leaflet to the normal level of the tricuspid annulus restores the right ventricular volume and provides better right ventricular morphology. In children, avoiding permanent fixation of the tricuspid annulus allows growth and flexibility of the annulus, which may contribute to the valve opening and closing mechanism.[21]

### Disadvantages

There is a risk of impairment of right ventricular function or of triggering ventricular arrhythmias due to interruption of some coronary arterial blood supply and/or of kinking of the right coronary artery. The stitches, therefore, have to be strictly endocardial and not penetrate the myocardium.

## MONOLEAFLET APPROACH WITHOUT PLICATION OF THE ATRIALIZED RIGHT VENTRICLE: SEBENING, AUGUSTIN AND DEARANI TECHNIQUE

### Technical Considerations

By using pledgetted horizontal mattress sutures placed through the dominant papillary muscles of the anterior leaflet and fixed to the interventricular septum, the anterior leaflet is "relocated." This keeps the free wall of the right ventricle and the anterior leaflet in apposition to the posterior aspect of the tricuspid annulus (Sebening stich). The posterior angle of the tricuspid orifice is plicated by bringing the right side of the anterior leaflet down to the septum[10,19] and a posterior annuloplasty is performed to narrow the diameter of the tricuspid annulus. To improve the stability of the annulus, an annuloplasty can be performed using a Teflon

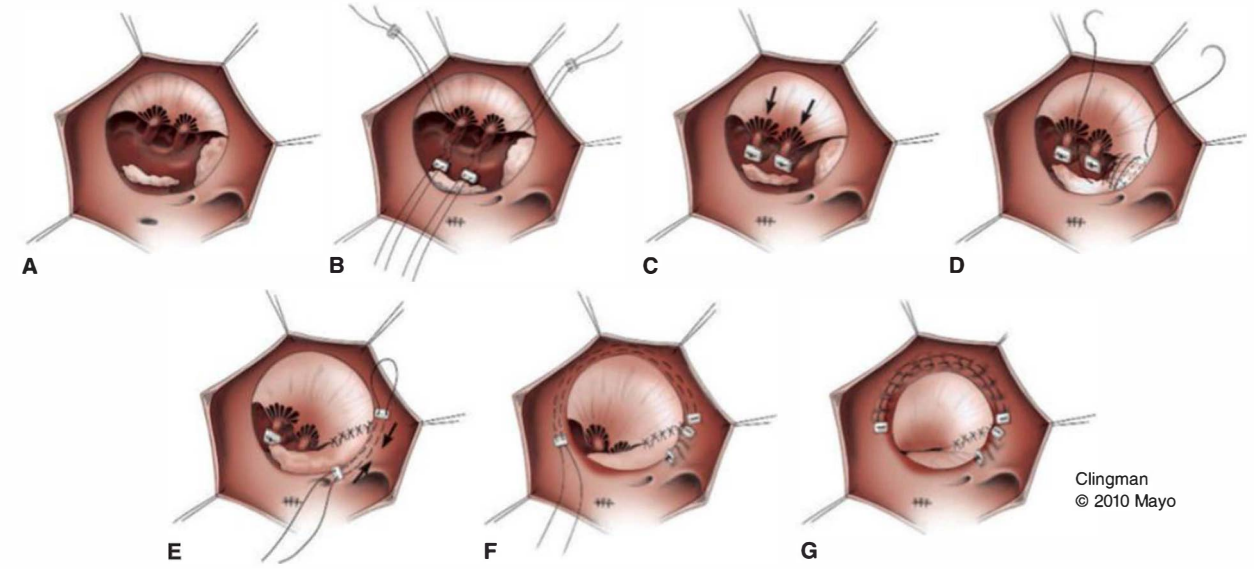



**FIGURE 85-8** Ebstein's morphology and Sebening/Dearani repair (**A**). The base of the papillary muscle is moved toward the ventricular septum (**B**, **C**). The posterior angle of the tricuspid orifice is closed by plication (**D**). A posterior annuloplasty (**E**) and a DeVega anterior purse-string annuloplasty (**F**, **G**). (Copyright and used with permission of Mayo Foundation for Medical Education and Research. All rights reserved)

strip.[6,19] An anterior purse-string annuloplasty (De Vega) should be considered if there is extensive dilatation of the anterior portion of the tricuspid annulus (Fig. 85-8).[10]

### Advantages

The base of the papillary muscle is brought toward the septum, improving geometry and function of the monoleaflet reconstruction. By avoiding plication, there is no risk of interrupting arterial blood supply of the right coronary artery. In some patients, the thin-walled, atrialized right ventricle maintains contractile, which may improve the function of the right ventricle.

### Disadvantages

By avoiding plication, the geometry and volume of the right ventricle are not altered. The nonfunctional portion (akinetic or dyskinetic) of the right ventricle is left in place.

## CORRECTIVE SURGERY FOR NEONATES AND YOUNG INFANTS

### Technical Considerations

A competent monocuspid valve is created using a variety of techniques, including the Sebening stitch, the longitudinal plication of the atrialized right ventricle, the posterior annuloplasty, the De Vega annuloplasty. The atrial septal defect is closed with a patch, leaving a 3-to-4-mm fenestration to unload the right heart and improve left ventricular cardiac output during the early postoperative period. If needed, the anterior leaflet can be taken down from the true annulus and enlarged with an autologous pericardial patch to create a large monocuspid valve. One might consider cone reconstruction as well. The management of associated pulmonary atresia depends on the adequacy of the tricuspid valve repair: If a competent tricuspid valve is achieved, a transannular pericardial patch is performed; otherwise a valved conduit is placed.[12,22]

### Advantages

The base of the papillary muscle is brought toward the septum, improving the geometry and function of the monoleaflet reconstruction. Longitudinal plication improves the geometry and function of the atrialized part of the right ventricle, providing more space for the lungs and reducing compression of the left ventricle, thus improving the left ventricular function.

### Disadvantages

This is high-risk surgery that is greatly dependent on the morphology of the anterior leaflet.

## UNIVENTRICULAR STRATEGY FOR NEONATES

If the tricuspid valve is not amenable to repair with highly laminated leaflet tissue, the tricuspid valve orifice is unguarded, the functional portion of the right ventricle is inadequate, or there is a right ventricular outflow tract obstruction that cannot be corrected reasonably, then the right ventricle is excluded (Starnes procedure) and a univentricular palliation strategy is undertaken.[23]

### Technical Considerations

Fenestrated (4 mm in ø) patching of the tricuspid valve is performed with a glutaraldehyde-fixed autologous pericardium sewn at the "anatomic" level of the tricuspid annulus, leaving the coronary sinus on the right atrial side. The atrial septum is resected and a reduction right atrioplasty is carried out. If the left ventricle is compressed, right ventricle plication or free wall resection[24] is performed. Care is taken to avoid kinking of the right coronary artery. If pulmonary regurgitation is present, the main pulmonary artery is ligated, creating iatrogenic pulmonary atresia. Pulmonary blood flow is provided by a modified Blalock-Taussig shunt.[23]

### Advantages

The procedure effectively decompresses the right side of the circulation, providing sufficient preload for the left ventricle.

### Disadvantages

The right ventricle exclusion procedure is a commitment to the single-ventricle pathway.

## TRICUSPID VALVE REPLACEMENT

### Technical Considerations

The abnormal leaflet tissue in the right ventricular outflow tract is excised in order to prevent obstruction. The valve suture line is diverted cephalad to the tricuspid annulus in the area of the membranous septum, AV node, and coronary sinus, to avoid injury of the conduction system and right coronary artery, leaving the coronary sinus to drain below the prosthesis.

Preferably, porcine bioprostheses are utilized due to their good durability; anticoagulants are not required, and access is permitted for catheterization, if necessary. A mechanical prosthesis is considered if the patient is already taking anticoagulants for another indication. The risk of thrombosis may increase even in the presence of effective anticoagulation, especially if significant right ventricular dysfunction is present.[25]

### Advantages

A competent valve.

### Disadvantages

Replacement should be used in older children or adults. Reoperation is inevitable due to structural failure of the valve. There are mechanical prosthesis-related complications if one is utilized.

## HEART TRANSPLANTATION

Orthotopic cardiac transplantation is considered as the first line of treatment only in the presence of severe biventricular dysfunction. Special consideration should be given to newborns with pulmonary atresia or stenosis and a thin-walled, poorly contractile right ventricle, which is most likely secondary to in utero severe tricuspid regurgitation. Ideally, these patients should be identified in utero and listed for transplant as soon as possible, otherwise, their prognosis is dismal.

## CONCOMITANT PROCEDURES

### "One and One-Half" Ventricle Repair

A bidirectional Glenn is an effective adjunctive procedure to any type of tricuspid valve reconstruction in patients with reduced function of the right ventricle, or when the tricuspid valve repair results in a small valvar orifice. This one and one-half ventricular repair provides unloading to an enlarged and dysfunctional myopathic right ventricle, with positive impact on tricuspid valve coaptation and preload of the left ventricle. By relieving the "pancake effect" of a massively dilated the right ventricle on the left ventricle, the compliance and diastolic function of the left ventricle improves. The significant reduction in mortality caused by right ventricular failure, the improvement in the function of the tricuspid valve, and decreasing risk of arrhythmias were demonstrated using the one and one-half ventricle repair technique.[26,27]

### Antiarrhythmic Treatment

Surgical treatment with intraoperative mapping and ablation are reserved for an unsuccessful percutaneous approach. Surgical ablation for accessory conduction pathways producing the Wolff–Parkinson–White syndrome and atrioventricular

nodal reentry tachycardia is highly successful, with nearly 100 percent freedom from recurrence. A concomitant maze procedure and cryoablation of the atrial isthmus for atrial flutter/fibrillation provide 75 percent freedom from recurrence.[28] Permanent pacing is required for <5 percent of the patients with Ebstein's anomaly, most commonly for atrioventricular block and rarely for sinus node dysfunction.[29] Epicardial placement of leads is preferable so as to not affect the function of the tricuspid valve.

## OUTCOMES

The unfavorable natural history[3] of patients with more severe forms of Ebstein's anomaly (worse functional status, cyanosis, severe tricuspid regurgitation, cardiothoracic ratio >0.6, right ventricular outflow tract obstruction, and early age at diagnosis) could be significantly improved with surgery. Reconstruction is feasible in the majority of patients, with low early mortality. The outcome, in terms of survival and freedom from reoperation in the long term is determined by the clinical state at the time of surgery. A timely operation is therefore warranted before cardiomegaly develops and the functional status deteriorates.[6] Excellent outcomes have been reported from various centers despite numerous types of repair (Table 85-1).

### Danielson and Dearani Techniques

Brown and coworkers[7] reported 5.9 percent early mortality for a cohort of 539 older patients (mean age 24 years) and 2.1 percent for patients operated after 2001. One hundred and eighty-two patients underwent tricuspid valve repair (either the Danielson or the Dearani technique was used) and 337 underwent tricuspid valve replacement. Late survival was 84.7 percent at 10 years and 71.2 percent at 20 years. Freedom from reoperation for valve repair and for valve replacement was 64 and 59 percent at 20 years, respectively. Tricuspid valve repair was associated with lower mortality and a lower reoperation rate, but patients who underwent valve replacement suffered more severely from the disease. In addition, significant residual tricuspid valve regurgitation persisted in 33 percent of patients who underwent valve repair, but only in 1 percent of patients who had undergone valve replacement.

### Carpentier Technique

Chauvaud[5] analyzed 269 operated patients (mean age 25 years) in whom 98 percent had undergone reconstructive surgery and 2 percent had had tricuspid valve replacement. The overall hospital mortality was 9 percent. A one and one-half ventricle repair was used in 107 patients, in whom the operative mortality decreased to 7 percent. Actuarial survival at 20 years was 80 percent. Eighty-four percent were classified as functional class I or II. Tricuspid valve insufficiency was nonexistent or trivial in 80 percent of patients, and reoperation was required in 9 percent of patients.

### Sebening and Augustin Techniques

Badiu and coworkers[6] reported 1.5 percent early mortality in 122 patients (mean age 23.8 years). In 110 (90.2 percent) patients primary tricuspid valve repair was feasible. Overall survival was 87.2, 85.1, and 81.2 percent at 10, 20 and 25 years, respectively. New York Heart Association functional class >II and cardiothoracic ratio of >0.6 were significant risk factors for mortality. Overall freedom from reoperation was 79.9, 61.9, and 58.0 at 10, 20 and 25 years, respectively. Age <12 years and a cardiothoracic ratio of >0.6 were significant risk factors for the need for reoperation.

### Cone Repair

Da Silva[4] reported 2.5 percent early mortality in 40 consecutive patients (mean age 16.8 years). Significant reduction in tricuspid regurgitation and good right ventricular morphology were demonstrated. No patient suffered from heart block. During the mean follow-up of 4 years, one patient died, two patients required late tricuspid valve re-repair, and exercise tolerance significantly improved in all patients. Similar results were reported by Wu[16]; there was no early or late death among 34 consecutive patients (mean age 17 years) who were operated on with the modified cone technique. Postoperative echocardiography showed no significant tricuspid incompetence in 29 patients and mild regurgitation in the remaining 5. The size of the right ventricle decreased significantly, accompanied by complete disappearance of the atrialized segment.

**TABLE 85-1: Outcomes of Repair of Ebstein's Anomaly**

| Author | Study Period | No. | Early Mortality (%) | Plasty (%) | 20-year Survival Rate (%) | OP-Technique |
|---|---|---|---|---|---|---|
| Brown et al. 2008[7] | 1972–2006 | 539 | 5.9 | 34 | 71 | Danielson & Dearani |
| Chauvaud et al. 2007[5] | 1980–2007 | 269 | 9 | 98 | 82 | Carpentier & Chauvaud 1½ ventricle |
| Badiu et al. 2010[6] | 1976–2007 | 122 | 1.5 | 90 | 85 | Sebening & Augustin |
| da Silva et al. 2007[4] | 1993–2005 | 40 | 2.5 | 100 | NA | Cone repair |

## One and One-Half Ventricle Repair

Excellent functional midterm outcomes were reported by Malhotra and coworkers[27] in 57 nonneonatal symptomatic patients with Ebstein's anomaly. A modified monoleaflet approach with selective bidirectional Glenn for ventricular unloading was used. No early or late deaths occurred. At the initial repair, three patients received a prosthetic valve. Four patients required reoperation for severe tricuspid regurgitation. At follow-up, all patients were acyanotic and in NYHA class I. Tricuspid regurgitation was mild or less in 49 (86 percent) and moderate in 6 patients (11 percent).

## Neonatal Repair

Only a few institutions perform biventricular neonatal repair, therefore, the data are very limited. Knott-Craig and coworkers[12] reviewed their experience with a two-ventricle repair in 22 severely symptomatic neonates and 5 young infants. Twenty-three patients underwent tricuspid valve repair, two underwent valve replacement, and two received a shunt. Hospital survival was 74 percent, with no late death during a median follow-up period of 5.4 years. Three patients required tricuspid valve replacement during the follow-up period. Late arrhythmia requiring medication was present in one patient. All patients were in New York Heart Association functional class I.

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## EBSTEIN'S ANOMALY BOARD REVIEW QUESTIONS (CHAPTER 85)

1. Which is correct regarding morphology of Ebstein's anomaly?
   A. The anterior and posterior leaflets are displaced toward the apex of the right ventricle.
   B. The redundant anterior leaflet has an abnormal attachment to the tricuspid annulus.
   C. There is a thin-walled atrialized component of the right ventricle.
   D. The functional component of the right ventricle consists of the apical and inlet portions.
   E. The outlet portion is small or even nonexistent.

2. Which is true regarding surgical management of subdivided atrium?
   A. Fifty percent of patients born with subdivided left atrium die in infancy without treatment.
   B. Urgent repair is indicated in older patients with chronic symptoms.

C. Hypothermic circulatory arrest is used in all patients with subdivided left atrium.
D. A left atrial approach is recommended for repair of subdivided left atrium in infants.
E. Percutaneous disruption of the obstructive membrane is the preferred approach in patients with subdivided right atrium.

3. Which is true regarding pathophysiology of Ebstein's anomaly?
   A. RV dilation can compromise LV function.
   B. Mild displacement of the tricuspid leaflets can obstruct pulmonary blood flow.
   C. Ductal flow increases RV afterload and has a positive impact on tricuspid valve function.
   D. Severe leaflet displacement results in functional tricuspid stenosis.
   E. Arrhythmias occur in 5 to 10 percent of patients.

4. Which is not a component of surgical repair of Ebstein's anomaly?
   A. Reconstruction of the tricuspid valve
   B. Plication of the atrialized right ventricle
   C. Enlargement of the interatrial septal defect
   D. Arrhythmia procedures
   E. Atrial reduction

5. Which is correct regarding outcomes after surgical repair of Ebstein's anomaly?
   A. Freedom from reoperation is less than 50 percent at 20 years after Danielson repair.
   B. Freedom from tricuspid insufficiency is 80 percent at 20 years after Carpentier repair.
   C. Freedom from reoperation is 70 percent at 20 years after Augustin repair.
   D. The right ventricular size does not decrease after the cone repair.
   E. Tricuspid insufficiency is mild or less in 50 percent of patients after one and one-half ventricle repair.

## ANSWERS

1. **Answer: C.** There is a thin-walled atrialized component of the right ventricle. The septal and posterior leaflets are displaced toward the apex of the right ventricle. The redundant anterior leaflet has a normal attachment to the tricuspid annulus. The functional component of the right ventricle consists of the apical and outlet portions, and the inlet portion is small or even nonexistent.
2. **Answer: B.** Urgent repair is indicated in an older patient with subdivided left atrium that presents with chronic symptoms. Up to 75 percent of patients will die without treatment during infancy. Hypothermic circulatory arrest is typically only used when there are associated complex anomalies. A right atrial approach is recommended for repair of subdivided left atrium in infants. A surgical repair remains the preferred approach for patients with subdivided right atrium.
3. **Answer: A.** RV dilation can displace the interventricular septum and compromise LV function. Mild displacement of the tricuspid leaflets does not adversely impact pulmonary blood flow, but severe displacement can cause severe valvular insufficiency. Ductal flow increases RV afterload and negatively impacts tricuspid valve function. Arrhythmias occur in 15 to 20 percent of patients.
4. **Answer: C.** The interatrial septal defect is closed, not enlarged. Other components of surgical repair include valve reconstruction, plication or resection of the right ventricle, procedures for control of arrhythmias, and reduction atrioplasty.
5. **Answer: B.** Freedom from tricuspid insufficiency is 80 percent at 20 years after Carpentier repair. Freedom from reoperation is 60 percent at 20 years after Danielson repair. Freedom from reoperation is 60 percent at 20 years after Augustin repair. The cone repair significantly reduces right ventricular size. Tricuspid insufficiency is mild or less in over 85 percent of patients after one and one-half ventricle repair.

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# Congenital Anomalies of the Sinuses of Valsalva and Aortico–Left Ventricular Tunnel

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## CONGENITAL ANOMALIES OF THE SINUSES OF VALSALVA

Initially described in 1839,[1] sinus of Valsalva (SoV) aneurysm is a rare condition incidentally found in 0.15 to 1 percent of patients undergoing cardiopulmonary bypass (CPB)[2,3] and five times more frequently in Asians.[4] In 1956, Morrow and Lillehei, using inflow inclusion and a membrane oxygenator, separately reported successful SoV aneurysm repair.[5,6] Since then, surgical repair has been established as the accepted standard of care.

Although acquired SoV aneurysms can occur in the setting of infection or trauma, they are most commonly congenital in origin and associated with many different connective tissue disorders, including rheumatoid arthritis, Ehlers–Danhlos syndrome, Marfan syndrome, Klippel–Feil syndrome, Turners syndrome, trisomies 13 and 15, Loeys–Dietz syndrome, arachnodactyly, and osteogenesis imperfecta. SoV aneurysms are frequently associated with other cardiac abnormalities, including ventricular septal defect (VSD) and aortic valve regurgitation.

SoV aneurysms most commonly originate from the right coronary sinus (RCS), followed by the noncoronary sinus (NCS),[7] reflecting the embryologic origin of the RCS and NCS from fusion of the bulbar septum and truncal ridges. Incomplete fusion of the bulbar septum can in fact result in aneurysm formation when the septum is subjected to long-standing systemic arterial pressure.[8] Aneurysms of the left coronary sinus are exceedingly rare and are usually an acquired phenomenon, as the left coronary cusp does not arise from the bulbar septum.

### Morphology

On histopathology, SoV aneurysms are characterized by separation of the sinus aortic media adjacent to the hinge point of the aortic valve cusp.[8] Normally, the sinuses are thinner than the tubular portion of the aorta and are limited inferiorly by the semicircular hinge point of the corresponding aortic valve cusp. In patients with SoV aneurysms, this otherwise normal characteristic is accentuated, and thinning of the aortic wall with disconnection of the media increases over time, resulting in aneurysm formation.[9]

The anatomic relationship between aortic root and adjacent cardiac structures predicts the clinical findings associated with gradual dilation and rupture of SoV aneurysms (Fig. 86-1). Aneurysms arising from the RCS most commonly involve the right atrium (RA) or right ventricular outflow tract (RVOT), while NCS aneurysms decompress either into the right or left atrium. Rare aneurysmal dilation of the left aortic sinus can eventually rupture into the left atrium. Although aortic root involvement is usually limited to a single sinus, enlargement of two sinuses or the entire aortic root occurs in rare cases. A concomitant VSD is found in up to 50 percent of congenital cases.[10,11]

### Clinical Features

SoV aneurysms produce symptoms by compression or direct rupture into an adjacent chamber and are often found incidentally. Onset of symptoms is gradual in 50 to 70 percent of patients and occurs most commonly between 20 and 30 years

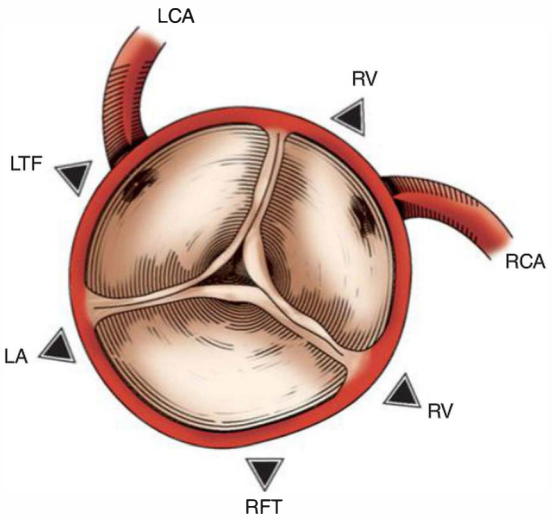



**FIGURE 86-1** Anatomic relationship between aortic root and adjacent cardiac structures as schematically viewed from the operating surgeon's perspective. LA, left atrium; LCA, left coronary artery; LFT, left fibrous trigone; RA, right atrium; RCA, right coronary artery; RV, right ventricle. (From Vricella LA, Cameron DE. Anomalies of the sinuses of Valsalva and aortico–left ventricular tunnel. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2006. With permission.)

of age but ranges in reported series from infancy to the seventh decade.[12–15] Aortic root rupture into either a neighboring cardiac chamber or within the pericardial cavity is rare in the first two decades of life.[16–18] Although clinical presentation is most commonly indolent, it can be acute depending on aneurysmal size, site of rupture (adjacent chamber versus pericardial sac), and the concomitant presence of a VSD or aortic insufficiency. In case of intracardiac rupture or fistulization, the most common presenting symptom is dyspnea, with nearly all patients exhibiting a continuous systolic–diastolic "machinery-like" murmur.[19] Numerous electrocardiographic findings have been described, including ST-segment depression, onset of Q waves, atrioventricular block, atrial fibrillation, and sudden death. Intrapericardial rupture typically presents with acute hemodynamic collapse and cardiac tamponade. A minority of patients (less than 20 percent) will present with evidence of sepsis associated with bacterial endocarditis.[20]

## Surgical Therapy

Urgent operative intervention is clearly indicated for symptomatic patients with rupture or compressive fistulas. SoV aneurysms that are asymptomatic but discovered at the time of CPB should be repaired because of the high likelihood of progressive increase in size, possibility of rupture, or symptom progression. Smaller, asymptomatic SoV aneurysms discovered incidentally during routine echocardiography can be safely followed over time unless progressive enlargement is noted or the patient develops symptoms. Surgical repair may be indicated earlier in patients with significant connective tissue disorder or family history of dissection or rupture.

After induction of general anesthesia, transesophageal echocardiography is routinely performed to confirm the preoperative findings, assess valvular competence, and rule out associated septation defects and endocarditic vegetations. Transesophageal echocardiography is also crucial in defining the course of the fistulous tract in case of intracardiac rupture. The surgical treatment of three-sinus enlargement of the aortic root is detailed elsewhere in this volume and entails either valve-sparing replacement[21,22] of the root or replacement with mechanical or biological prostheses.

Aortotomy is performed to assess the aortic root anatomy and an additional right atriotomy is performed to expose the distal site of rupture or protrusion, especially the "windsock" aneurysmal sac that projects toward the right-sided chambers. A transventricular approach can be utilized alternatively to expose a concomitant VSD. The aortic aspect of the defect is repaired with prosthetic material (Fig. 86-2) to prevent the high risk of aortic valve distortion and recurrence of primary closure. In case of diverticular extension into the RA or right ventricle (RV) (via a VSD), the distal aspect of the SoV aneurysm is corrected with similar technique.

In spite of several well-described repair techniques, the incidence of aortic regurgitation (AR) has been reported between 30 and 50 percent and is severe enough to warrant aortic valve replacement (AVR) in as many as 50 to 80 percent of affected patients.[23] AR commonly results from prolapse of the affected sinus cusp, which occurs secondary to involvement of the annulus, loss of infundibular support with a conal VSD, or a Venturi effect on the involved cusp.[18] The Ross procedure is considered a viable alternative to root replacement in selected cases.

## Results

Au and coworkers presented the long-term results of 53 patients treated for SoV aneurysms, reporting no operative mortality and a 15-year survival of 83 percent.[14] A retrospective review of 22 patients presenting with intracardiac rupture at the Johns Hopkins Hospital demonstrated an operative mortality of 5 percent, with late survival of 85 and 60 percent at 5 and 10 years, respectively.[19] This decrease in late survival likely reflects the noncongenital etiology of SoV aneurysm more frequently observed in western countries. Although factors such as bacterial endocarditis, need for AVR, and VSD closure do not appear to worsen survival, preoperative AR and VSD have been reported to decrease aortic valve-related freedom from reintervention, with a reported need for AVR of up to 25 percent in the decade following diagnosis and initial intervention.[13,14,24]

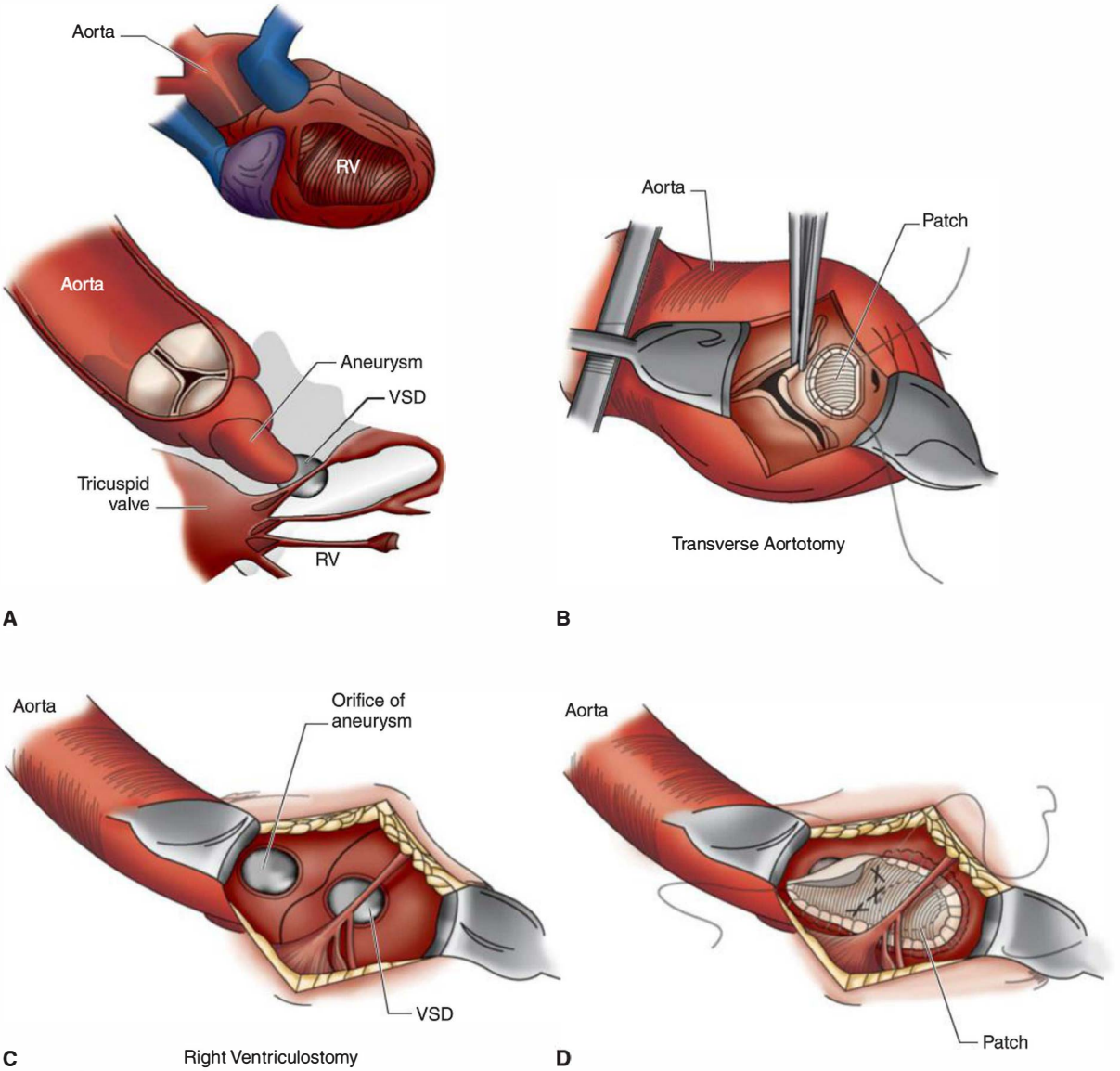



**FIGURE 86-2** Surgical repair of aneurysm of the sinus of Valsalva, originating from the right coronary sinus. **A.** Schematic view with aneurysm protruding through ventricular septal defect. **B.** The inlet to the aneurysm is closed with a patch of bovine or autologous pericardium. **C** and **D.** Transventricular repair of the inferior portion of the sinus of Valsalva aneurysm. The defect and the orifice of the aneurysm are closed with a single polyester patch. RV, right ventricle; VSD, ventricular septal defect. (From Vricella LA, Cameron DE. Anomalies of the sinuses of Valsalva and aortico–left ventricular tunnel. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2006. With permission.)

## AORTICO–LEFT VENTRICULAR TUNNEL

Aortico–left ventricular tunnel (ALVT) is an extremely rare developmental condition consisting of a paravalvular communication between the aortic root and left ventricular cavity. It represents only 0.001 percent of all congenital cardiac anomalies.

### Morphology

The lesion typically originates from the RCS around the coronary ostium and can be appreciated grossly as a palpable, pulsatile mass between aortic and pulmonary artery roots. The course of the aneurysm can be variable, but it usually terminates in the ventricular cavity below

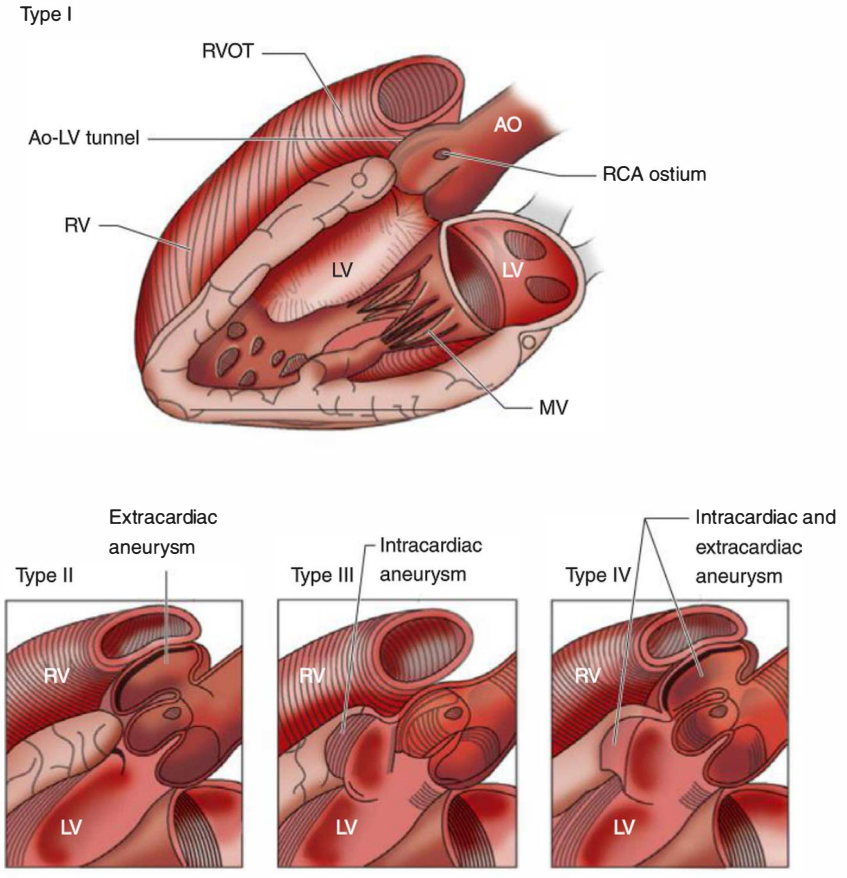



**FIGURE 86-3** Proposed morphologic classification of aortico–left ventricular (Ao-LV) tunnel. Type I: Simple tunnel with slit-like opening at aortic end, no aortic valve distortion. Type II: Large tunnel with oval aortic opening with or without aortic valve distortion. Type I II: Intracardiac aneurysm of the ventricular portion of the tunnel with or without right ventricular outflow tract obstruction. Type IV: Combination of types II and III. (From Shum-Tim D, Tchervenkov CI. Aortic–left ventricular tunnel. In: Mavroudis C, Backer CL (eds). *Pediatric Cardiac Surgery,* 3rd ed. Philadelphia: Mosby, 2003:576. With permission.)

the right coronary leaflet. The ventricular opening can be appreciated with retraction of the aortic valve cusps. The most frequently occurring anatomic variants are categorized in the Hovaguimian classification (Fig. 86-3).[25] Almost half of all patients will disclose associated defects (VSD, bicuspid aortic valve) on echocardiographic examination, although the aortic valve is usually competent. Coronary anomalies have been reported in up to one-third of patients.[6]

## Clinical Features

The clinical presentation is dependent on the size of the fistulous tract and the degree of associated AR. Although an ALVT is an uncommon cause of neonatal congestive heart failure, ALVT should be suspected in neonates with plethoric lung fields, cardiomegaly, a diastolic murmur, and widened pulse pressure. Like SoV aneurysms, large fistulous tracts can also lead to progressive right ventricular outflow tract obstruction and cyanosis.

The diagnostic modality of choice is transthoracic echocardiography, which readily demonstrates the classic "drop-out" of the interventricular septum inferior to the RCS. Cardiac catheterization and magnetic resonance imaging are rarely required.

## Therapy

The degree of valvular insufficiency and severity of congestive heart failure often mandate immediate operative intervention, but serial observation with echocardiography is acceptable, as spontaneous closure of small ALVT defects has been reported.

Intraoperatively, bicaval cannulation is employed only if a concomitant septal defect requires surgical correction. Cardiopulmonary bypass with moderate hypothermia

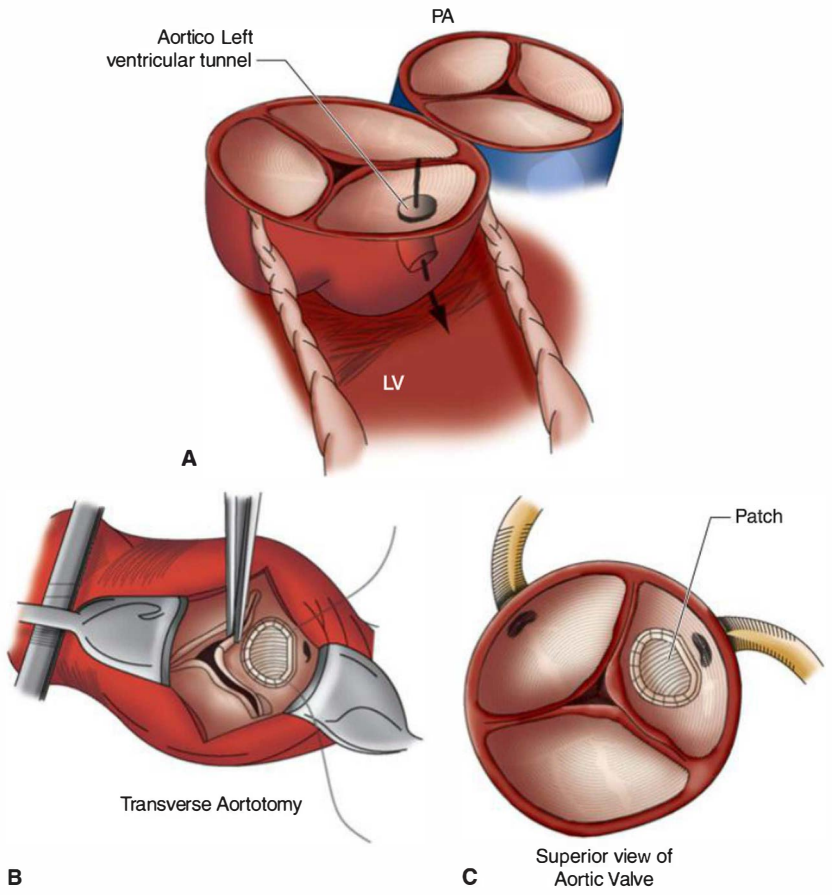



**FIGURE 86-4** Aortico–left ventricular tunnel with the inlet originating (**A**) in the right coronary sinus (most typical location). Through an aortotomy (**B** and **C**), the inlet orifice to the tunnel is closed with an autologous pericardial patch. The ventricular opening of the tunnel is closed through the aorta separately, either primarily or with an additional patch. (From Vricella LA, Cameron DE. Anomalies of the sinuses of Valsalva and aortico–left ventricular tunnel. In: Kaiser LR, Kron IL, Spray TL (eds). *Mastery of Cardiothoracic Surgery,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2006. With permission.)

and the direct infusion of coronary ostial cardioplegia are employed. We favor closure of both inlet and outlet orifices of the tunnel in a manner similar as that described for SoV aneurysm (Fig. 86-4). Patch closure of both openings of the ALVT provides additional protection from late valvular regurgitation and recurrence of the fistulous tract. As an alternative approach, both orifices of the ALVT can be approached from within the ALVT (Fig. 86-5).

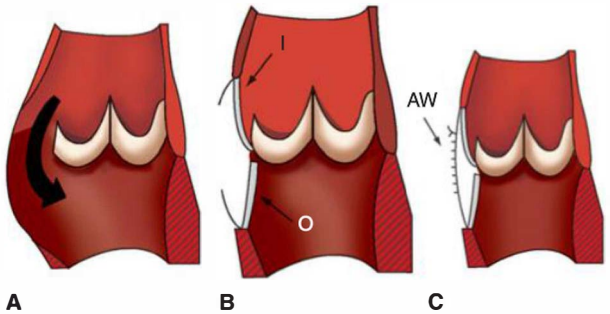



**FIGURE 86-5** Schematic representation of alternative approach for repair of aortico–left ventricular tunnel. **A.** Cross section of the aortic root with the tunnel indicated by the downward-pointing arrow. **B.** The tunnel is exposed *directly* through an aortotomy, and the inlet (I) an outlet (O) orifices are closed with separate patches. **C.** The aortic wall (AW) is closed primarily.

## Results

In contemporary series, operative mortality has been reported to be less than 10 percent, with need for reoperative intervention being the most significant determinant of late outcome. The most common early complications include atrioventricular heart block and aortic valve regurgitation. AR secondary to postrepair deformity or root dilation due to lack of annular support around the ALVT may result in need for late aortic valve or root replacement in up to 50 percent of patients, particularly if initial correction is delayed b eyond infancy.[26,27]

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# Extracorporeal Membrane Oxygenation in Pediatric Cardiac Care

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## INTRODUCTION

From the earliest days, advances in extracorporeal membrane oxygenation (ECMO) have been linked to advances in cardiopulmonary bypass (CPB) and repair of congenital cardiac malformations. Since C. Walton Lillihei[1] first employed the technique of controlled cross-circulation using the patient's parent, efforts to perfect cardiopulmonary support have transitioned from the operating room to the intensive care unit. In the intervening years, every facet of CPB has been studied and refined. Improvements in these techniques have afforded the surgeon the opportunity to tackle the most complex anatomic anomalies in even the smallest babies. Likewise, advances in extracorporeal support (ECLS) methods have led clinicians to expand their clinical indications and implementation in the ICU. However, despite the fact that the notion and use of extracorporeal circulation originated in the cardiac surgical suite, heart disease was, until the last decade or so, usually a contraindication for ECMO. Early experience in adults was discouraging,[2] with better success reported in the care of newborns with respiratory failure.[3] Extension to include older infants and children with respiratory failure followed.[4]

Pediatric cardiac ECMO, as it has come to be known, was first reported by Soeter and colleagues in 1973. He described the successful application of ECMO in a 4-year-old girl following repair of tetralogy of Fallot, who was weaned from support in 48 hours and discharged home 11 days later.[5] By the late 1980s and early 1990s, cardiac ECMO gained traction in the pediatric cardiac community, as many large centers reported favorable outcomes with postoperative support. With experience, refinement, and successes, cardiac ECMO has made the transition from "rescue" therapy, to "therapeutic" or even "preventive" management. Coincident with advances in pharmacologic and mechanical ventilatory support strategies for respiratory failure, the number of ECMO runs for the cardiac population has steadily increased as a proportion of the Extracorporeal Life Support Organization (ELSO) Registry (Fig. 87-1). In this chapter, we take a comprehensive look at cardiac ECMO, with attention to the different types (venoarterial or venovenous), their relative indications, and their respective advantages, disadvantages, and outcomes. In addition, we discuss the myriad equipment options and also review the physiology of ECMO and principles of clinical application. Last, we consider new opportunities and indications for mechanical circulatory support.

## VENOARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION

In simplest terms, venoarterial ECMO (VA-ECMO) consists of taking deoxygenated blood from the venous circulation, oxygenating it, and then pumping it back into the arterial circulation. How this is accomplished depends on individual and institutional experience and preference. The obvious benefit is that the patient's entire cardiorespiratory system is bypassed, thereby ensuring adequate end-organ oxygenation despite respiratory and circulatory collapse. Ideally, the brain, kidneys, and other organs thereby maintain their essential functions in a circumstance that would otherwise almost surely lead to multi-organ failure and possibly death. Importantly, this support system likely creates an environment that is more conducive to functional improvement. There are ample data to support this assertion with regard to

the lungs, and advances in the understanding of the pathogenesis of cardiac failure suggest that the same is likely true for the heart.[7]

## Indications and Experience

Broad indications for VA-ECMO include preoperative stabilization, postcardiotomy support, bridge-to-transplant, cardiopulmonary arrest, myocarditis and cardiomyopathy, pulmonary hypertension, intractable arrhythmias, and occasionally, respiratory failure refractory to venovenous extracorporeal circulatiry support.

### PREOPERATIVE SUPPORT

Among neonates and pediatric patients, congenital heart disease is by far the most common indication for VA-ECMO,

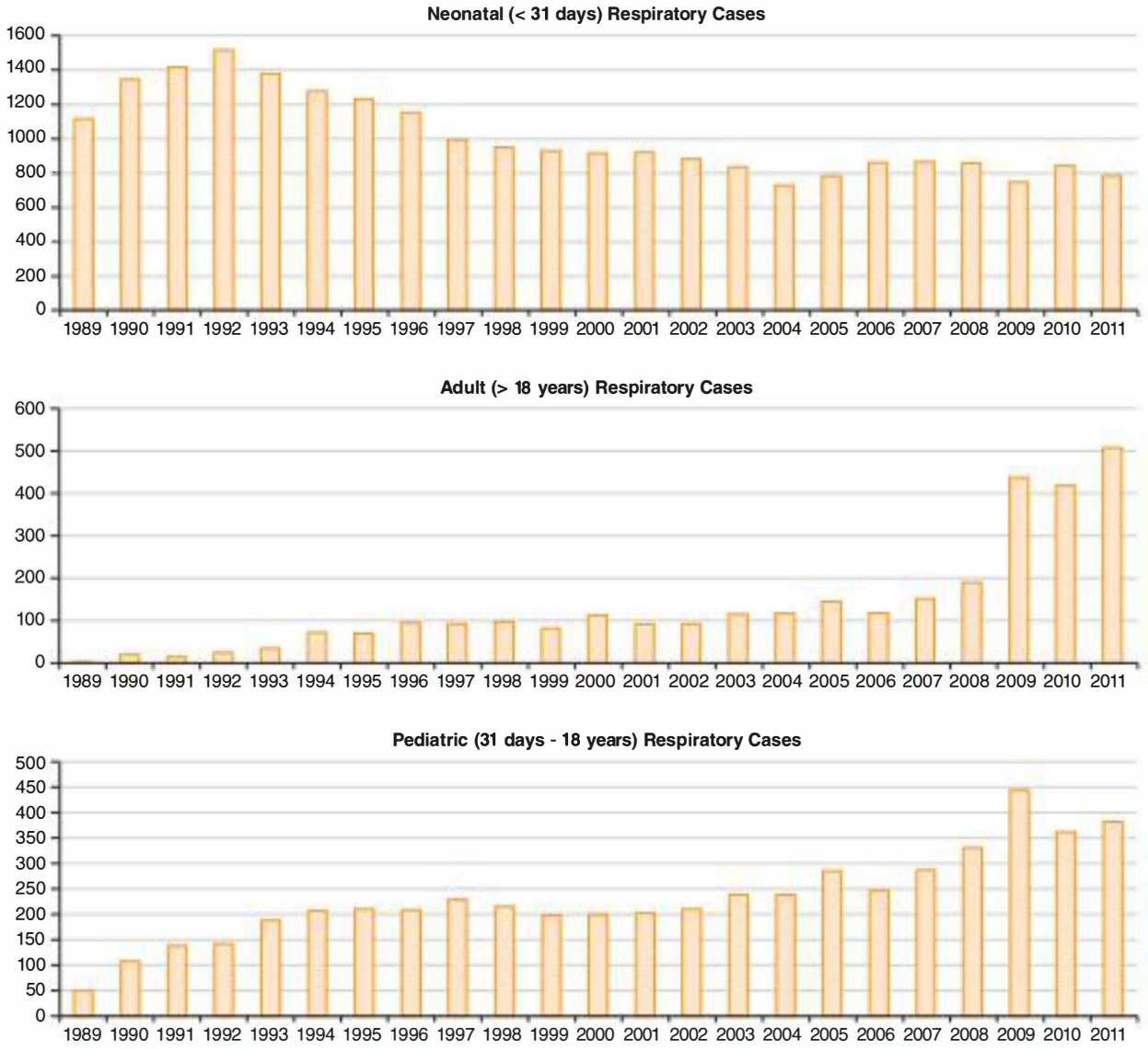



**FIGURE 87-1** Annual cardiac and respiratory ECMO volumes, segregated by patient age.

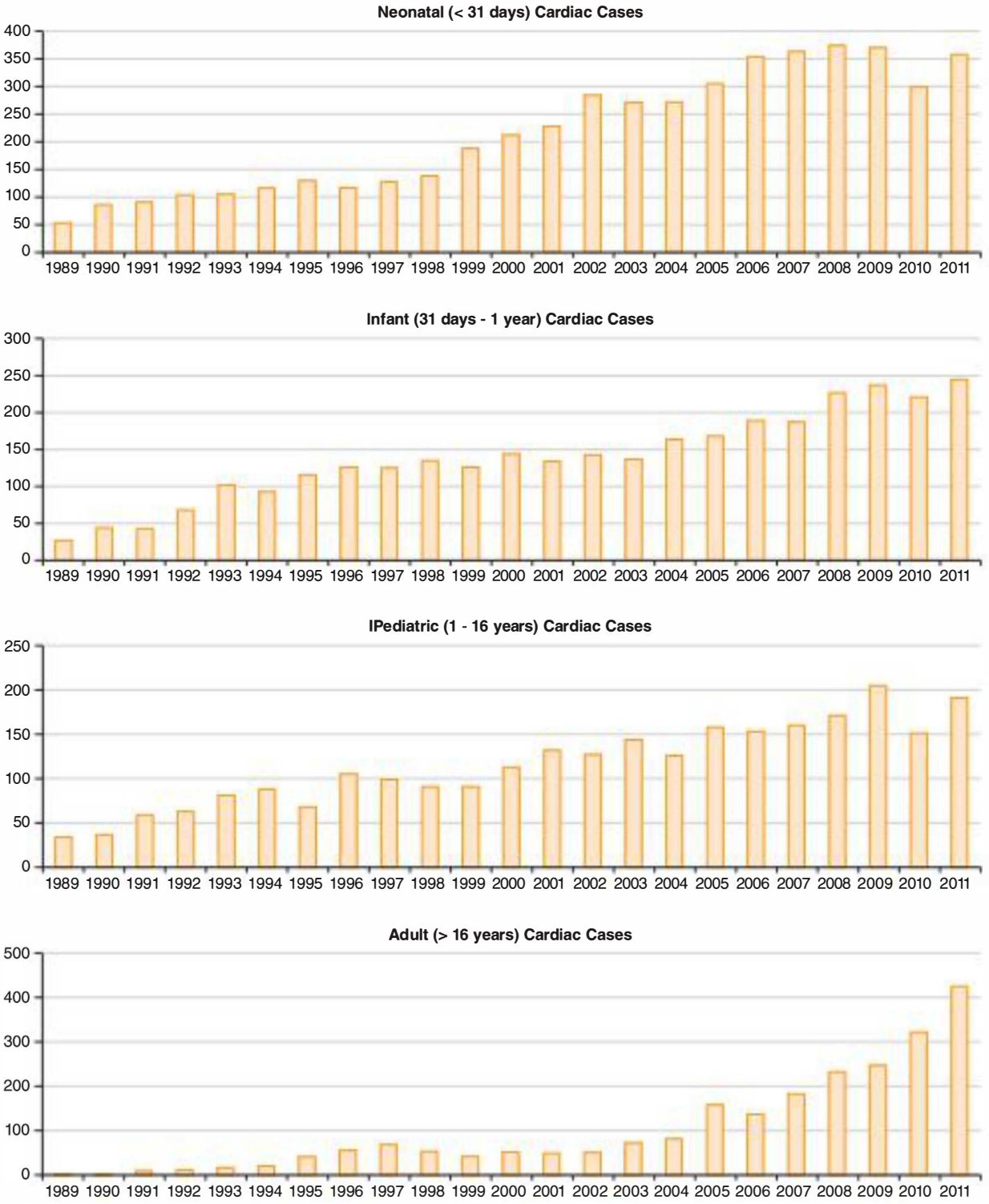



**FIGURE 87-1** (*continued*)

accounting for 72 percent of all cases, and 86 percent of neonatal (age <31 days) cases.[6] In neonates with congenital cardiac malformations, indications for VA-ECMO can arise soon after birth. The infant with obstructed total anomalous pulmonary venous drainage is the classic example of a newborn that can present in extremis and require emergent institution of VA-ECMO. Ideally, with VA-ECMO support, the baby's clinical condition can be optimized prior to surgical correction. Similarly, some neonates with congenital cardiomyopathy (i.e., dysrhythmias) will benefit from support while diagnostic studies and therapeutic interventions, such as radiofrequency ablation, are pursued. Without ECMO, these babies might die before a diagnosis is established and therapies implemented.

## POSTOPERATIVE SUPPORT

Postoperative instability is the most common indication for VA-ECMO in the cardiac setting. Whether due to prolonged CPB or circulatory arrest times, complex surgical repair and manipulation of the heart, exaggerated inflammatory response to CPB, or inadequate myocardial protection, the availability of VA-ECMO is often lifesaving as a bridge to recovery. Of course it is critical that residual structural lesions be ruled out as the cause for compromise; thus a thorough assessment (i.e., transesophageal echocardiogram) is imperative before initiating VA-ECMO. Standard postoperative ECMO must be distinguished from rapid or resuscitative ECMO (eCPR), a topic covered later in the chapter.

In 1987, Kanter and colleagues were the first to report some success with ECMO in patients who had undergone cardiotomy, with 6 of 13 surviving to discharge.[8] Since then, the literature is replete with institutional reports of ECMO use in patients with structural cardiac anomalies. Morris and coworkers at the Children's Hospital of Philadelphia (CHOP) reported their experience with 137 patients on cardiac ECMO[9] between 1995 and 2001. Diagnoses encompassed the spectrum of congenital cardiac malformations, including single ventricle with intracardiac mixing and single ventricle with separate circulations, as well as children with structurally normal hearts. Overall survival to discharge was 39 percent. Two-thirds of the patients had undergone cardiac surgery prior to ECMO, with 40 percent of those surviving to discharge. In that subset, risk factors for mortality included age less than 1 month, male gender, duration of mechanical ventilation before initiation of ECMO, and the development of renal or hepatic dysfunction on ECMO. Failure to separate from CPB was not found to be a predictor of death, which means that in those cases ECMO was literally life-saving. In addition, despite historical bias against placing patients with single ventricle physiology on ECMO, this factor did not prove to be significantly associated with death in this series. No factor analyzed was predictive of mortality in the subset of patients who had not undergone surgery and in whom survival to discharge was 35 percent. Overall, considering the fact that many of the survivors likely would have died without mechanical support, the authors concluded that, "it is imprudent to impose strict indications or contraindications to ECMO support."

Sivarajan and colleagues reported another large study of 116 patients supported with cardiac ECMO from Royal Children's Hospital in Melbourne. They included data from patients undergoing conventional ECMO as well as patients cannulated during eCPR. Survival to hospital discharge improved from 33 percent in the earlier era (1990–2001), to 48 percent in the recent era (2002–2006).[10] Another relatively large series from the Great Ormond Street Hospital in London reported on 81 cardiac patients managed with ECMO between 1992 and 2000.[11] More than half of these patients were placed on ECMO in the OR following multiple unsuccessful attempts at separation from CPB. Overall survival to discharge was 49 percent. Their report includes only patients with two-ventricle anatomy. Patients placed on ECMO in the surgical suite had a 64 percent survival to discharge, as compared to 29 percent in those patients cannulated in the ICU. They found, in agreement with many previous studies, that renal failure was a significant risk factor for mortality. Also, as with virtually all other reports of pediatric cardiac ECMO, their data support the contention that a residual cardiac lesion bodes poorly for outcome and is a contraindication for initiation of support. In our experience, however, there are situations where a patient can be supported for a period of hours or even days, subsequently return to the operating room or the interventional cardiology suite for correction of residual lesions, and then be weaned from ECMO; so even this contraindication is a relative one.

VA-ECMO can also be utilized for postoperative support following heart transplantation, either for the treatment of pulmonary hypertension or early graft dysfunction. Galantowicz and Stolar[12] reported 40 percent salvage rate among children requiring mechanical support following transplantation. Rarely, acute rejection episodes occurring remotely that are marked by severe myocardial dysfunction can be managed with VA-ECMO until the initiation of antirejection therapy.[13]

## BRIDGE-TO-TRANSPLANTATION OR BRIDGE-TO-BRIDGE

VA-ECMO can also be indicated in neonates and pediatric patients with cardiac failure waiting for transplantation, or more rarely, as an intermediate step prior to implantation of a ventricular assist device[14]. A recent series by Imamura et al.[15] at Arkansas Children's Hospital reported 43 percent mortality among 21 patients supported with ECMO as a bridge-to-transplant. The ELSO registry reported similar data, with 51 percent mortality for pediatric patients supported with ECMO prior to transplantation.[16]

Data from a large single-institution study from CHOP had comparatively better outcomes. These authors described 31 patients supported with ECMO as a bridge to cardiac transplantation.[17] No difference in long-term survival was found between heart transplant recipients who were supported with ECMO prior to transplant versus those who

were not. Of the 31 patients, 6 had sufficient recovery of function to be weaned from ECMO and discharged home ("bridged to recovery"), while 12 of the original 31 ultimately underwent cardiac transplantation. Overall survival to discharge was 48 percent (15 of 31).

The CHOP experience does not support the enforcement of an arbitrary cutoff for duration of support, as they have had several patients survive after more than 250 h on ECMO, including four who were successfully transplanted after 500 h of support and one who survived 1126 h before transplant. Furthermore, as others have reported, pre-ECMO cardiac arrest was not associated with poorer outcome.[18–20]

For patients requiring ECMO after cardiac transplantation, Kirshbom and coworkers[17] reported 22 percent survival to discharge in those patients requiring support soon after transplantation as compared to the three patients who required support in the late period; two of the latter survived to discharge. They concluded that ECMO can be an effective tool for management of the peritransplant patient.

Morales and colleagues reported the initial multicenter experience with the Berlin Heart EXCOR ventricular assist device in 73 patients from 17 institutions.[14] VA-ECMO was used as a bridge to EXCOR in 22 patients (33 percent). Though the overall mortality for the cohort was high at 24 percent, patients supported with ECMO prior to device implantation were not an increased risk for death. ECMO was therefore used successfully as a bridge-to-bridge in these patients. ECMO could also be applied as a "bridge-to-decision" in neonates in whom the decision to proceed with EXCOR implantation or heart transplantation is unclear for social, neurologic, infectious, or other reason. This is similar to the paradigm for application of short-term mechanical circulatory assist devices in older patients and adults.

## Rapid or Resuscitative Extracorporeal Membrane Oxygenation (eCPR)

*eCPR* refers to the application of ECMO as an immediate life-sustaining therapy in the setting of cardiopulmonary arrest. Most centers consider activation of an eCPR protocol after 10 min of resuscitation, or after two rounds of "code" drugs have been administered without success.[21] John Gibbon, the pioneer of CPB, speculated in 1939 on the ability of a heart–lung machine to temporarily take over the function of the heart and lungs during a period of deterioration and provide a time interval for the recovery of organ function, leading to potential survival.[22] eCPR has evolved from early reports of use following myocardial infarction, pulmonary embolism, and other emergency conditions.[23–26]

The acceptance of eCPR as a viable therapeutic intervention has been largely based on the study by Duncan and colleagues,[27] demonstrating that patients cannulated for eCPR had equivalent survival to patients cannulated for conventional cardiac ECMO. Its current form is the result of a slow iterative approach in the design and development of both the equipment and management principles over the past 20 years.

Though specific components may differ among institutions, successful application of eCPR generally requires the coordinated 24-hour involvement of surgical, nursing, perfusion, and ICU staff, as well as a modified ECMO circuit that can be primed and deployed rapidly (ideally within 15 min). A state-of-the-art rapid deployment circuit ideally would include a preassembled completely heparin-coated (Carmeda® Bio-Active Surface) surface, a centrifugal blood pump, a new-generation hollow-fiber oxygenator such as the Quadrox® or Minimax® oxygenator (approximately 250 mL priming volume), a Bio-Probe flow probe, and a BioTrend Oxygen Saturation and Hematocrit monitor. The entire circuit can be assembled and primed in under 5 minutes.[28] eCPR usually necessitates institution of VA-ECMO, with cannulation sites individualized to anatomy and postoperative status, and often patients are actively cooled for 48 hours to 34°C to lower metabolic demands and provide central nervous system (CNS) protection. Based on current literature, it is unclear whether the duration of conventional CPR should limit the application of ECMO. A recent study from Kane et al. showed no difference in survival based on conventional CPR duration.[21] Further, there are data demonstrating survival even after prolonged (>95 minutes) CPR.[29,30] On the other hand, however, a study by Sivajaran et al.[10] showed a clear survival disadvantage in patients undergoing ≥30 minutes of conventional CPR. It is also likely that other risk factors such as high lactate levels or low arterial pH, which have more consistently been uncovered, could be surrogates for prolonged conventional CPR duration. Neurologic status is intuitively influenced by prolonged CPR, and further studies will be required to elucidate optimam timing and prognostic factors implicit in these outcomes.

Despite the controversies regarding the specific criteria and development of eCPR protocols, there is clear evidence that eCPR is a useful and important strategy to salvage patients who would otherwise die. The study by Kane et al.[21] from Boston Children's Hospital reported their outcomes in 172 patients with cardiac disease undergoing eCPR between 1995 and 2008. They reported a laudable 51 percent survival to discharge, which was independent of anatomy, CPR duration, and location of cardiac arrest. Importantly, 75 percent of the survivors had either no or mild neurologic impairment as measured by pediatric overall performance category (POPC) and pediatric cerebral performance category (PCPC) scores ≤2. Data from another large series at the Hospital for Sick Children in Toronto,[30] which included prolonged conventional CPR duration of up to 95 minutes, also demonstrated the efficacy of eCPR, with 30 percent survival. These authors concluded that the lack of consistent poor prognostic factors in eCPR should prompt aggressive application of resuscitative ECMO in all patients without obvious contraindications. Institution of an eCPR protocol, as mentioned previously, requires a tremendous amount of resources, personnel, as well as a dedicated iterative approach to refining deployment. An additional caveat is that centers offering eCPR should possess both transplant and longer-term mechanical

circulatory assistance capabilities as an important (up to 11 percent) of eCPR patients will eventually require one of these exit strategies.[21,30]

## PATIENT SELECTION AND TIMING OF VENOARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION

Defining which patients are appropriate candidates for cardiac ECMO support is complicated, and is evolving as the utilization of cardiac ECMO increases. Specific conditions including incurable malignancy, advanced multisystem organ failure, extreme prematurity, and severe neurologic or CNS damage constitute absolute contraindications for the application of mechanical support.[31]

Based on univariate and multiple logistic regression analysis of retrospectively collected data in 218 patients, Trittenwein and colleagues proposed inclusion criteria related to lactate and central venous oxygen saturations.[32] We believe that such criteria are too narrow and not universally applicable. As mentioned above, establishment of rigid inclusion and/or exclusion criteria is problematic; each case requires thoughtful consideration on an individual and institutional basis.

Timing of initiation of ECMO is critically important. Low-cardiac-output syndrome (LCOS)[33,34] is common to most scenarios in which cardiac ECMO is considered. Clinically, LCOS manifests as poor peripheral perfusion, oliguria, and lactic acidosis despite adequate intravascular volume and often elevated filling pressures. Mixed venous oxygen saturations are low, secondary to decreased oxygen delivery. After correcting for anemia, hypoxia, or obstructive cardiac disease, traditional therapy for this type of cardiogenic shock focuses on maximizing pharmacologic support. Usual agents act through a variety of mechanisms, but most cause an increase in biventricular afterload and heart rate. The net effect is to increase myocardial work and oxygen demand in a setting where myocardial oxygen supply is already compromised. This can exacerbate injury and delay or even prevent myocardial recovery. With ECMO, unloading the heart and decreasing its work creates an environment that is more favorable for repair and recovery.[35] In effect, earlier institution of mechanical support helps to ensure adequate perfusion of the heart, brain, kidneys, and other vital organs while minimizing ongoing myocardial insult and enhancing recovery. Most recent reports have documented better outcomes in those patients placed on ECMO in the OR as compared to those cannulated in the ICU.[11,18,36] Along these lines, Shen et al. reported 87 percent hospital survival in 23 patients who were routinely converted directly from CPB to VAD support in the OR after undergoing the Norwood procedure.[37] Although many of these patients would likely have survived without circulatory support, the authors assert that some patients might have otherwise developed acute heart failure and therefore benefited from early implementation of mechanical cardiac assistance, especially in the setting of hypoxemia that is associated with all Norwood patients. Research has demonstrated that in the setting of hypoxemia, the brain is extremely vulnerable to diminished cerebral oxygen delivery that can accompany a fall in systemic cardiac output.[38]

Experience with mechanical support of nonsurgical heart failure also merits consideration. In their series, Morris and associates report 35 percent survival in the nonsurgical population, which included patients with cardiomyopathy and myocarditis.[9] Marx and coworkers have reported 67 percent survival in patients supported with ECMO for acute myocarditis and 62 percent survival in patients with cardiomyopathy. Duncan and colleagues report 83 percent survival in 12 pediatric patients with myocarditis who were placed on ECMO.[34] Of their overall population (12 ECMO, 3 VAD), 47 percent recovered with return of native ventricular function, and 33 percent survived following successful ECMO bridge to cardiac transplantation.

## COMPLICATIONS ASSOCIATED WITH VENOARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION

Survival is not the only marker of a successful ECMO run. Long-term sequelae can be considerable and devastating and should bear considerable weight in any discussion of indications and outcomes. Assessment of neurologic insult directly related to cardiac ECMO is difficult due to the many confounding variables. Cyanotic heart disease alone is, as an example, associated with neurodevelopmental abnormalities.[39–42] Similarly, behavioral and cognitive impairment are well-documented in both adults and children following CPB, as are gross and fine motor deficits.[43–45] In addition, follow-up in neonatal respiratory ECMO survivors has revealed neurobehavioral and functional deficiencies.[46–54]

Acute abnormalities have been described in cardiac ECMO patients at the University of Michigan, as 14 percent had seizures and 7 percent had radiographic evidence of injury to the CNS.[18] Hamrick and colleagues report significant long-term impairment in their 11-year experience with infants supported by ECMO following cardiac surgery.[55] Of their 53 patients, 7 of the 14 survivors available for long-term follow-up (13 percent overall) were neurologically completely intact.

Golej and Trittenwein have looked critically at the issue of neurologic impairment associated with cardiac ECMO.[56] They advocate for early recognition and rehabilitation in this at-risk population. As with most advances in CPB and operating room management, monitoring devices and strategies are crossing over into the ICU (bi-spectral index monitoring and near-infrared spectroscopy). However, pre-ECMO intracranial imaging is not as universally possible in cardiac patients as it is in neonates with respiratory failure. In that population, evidence of preexisting intracranial hemorrhage is a contraindication for ECMO. In cardiac ECMO patients, serial cranial ultrasounds are routinely obtained after return to the ICU, but even these studies lack adequate capability to detect anything less than gross hemorrhage or infarct.[55] Refinements in the ECMO circuit and devices have allowed

for relative minimization of anticoagulation needs (discussed later), but the risks of hemorrhage and embolic events remain real and may be even more significant on a microvascular level than is currently appreciated.

## Implementation

Placing a patient on ECMO for cardiac support requires a cohesive team of surgeons, perfusionists, ECMO specialists, nurses, and cardiac intensivists. Though conceptually simple, ECMO cannulation is fraught with potential technical complications that are magnified by critical patient condition and need for expeditious completion. Experience and vigilance therefore are critical to ensuring optimal outcomes.

## Cannulation

The cannulation strategy for ECMO must be based on the type of support to be provided (VA-ECMO vs VV-ECMO), the age and weight of the patients, and underlying structural or functional cardiac abnormalities. When providing complete cardiopulmonary support (VA-ECMO), the arterial cannula is generally introduced into the ascending aorta, right common carotid artery, or either femoral artery. Other cannulation sites occasionally may be used depending on unique anatomic considerations. The importance of proper cannula selection and quality of the cannulation to successful ECMO support cannot be overemphasized. The right common carotid artery is generally the ideal site for peripheral arterial cannulation in neonates and infants because of the vessel's diameter and the fact that relatively direct access to the right atrium makes the right internal jugular vein the optimal site of venous cannulation. The optimal cannula size must take into consideration the size of the carotid artery and the projected amount of blood flow through the cannula. Cannulation with an oversized cannula should be avoided to prevent injury to the carotid endothelium or complete and catastrophic vascular disruption. The cervical arterial cannula is inserted into the common carotid under direct vision using a limited neck incision. The cannula is advanced so that the tip lies at the base of the innominate artery. It is important to avoid advancing the cannula too far into the aorta to prevent partial occlusion of the aortic arch, injury to the facing aortic wall, or retrograde orientation of the cannula into the ascending aorta. The latter puts unnecessary mechanical stress of the aortic valve that may lead to injury to the delicate valve leaflets or valvular insufficiency. When cannulating the carotid artery, the surgeons should consider the potential for carotid reconstruction once ECMO support is discontinued. Although prior neck cannulation does not preclude subsequent use of the carotid artery, occlusion of either carotid artery is an obvious contraindication to cervical arterial cannulation. Carotid artery reconstruction at the time of decannulation can be performed if cannulation techniques are employed that are conducive for this. Several reports have demonstrated very good short- and long-term patency following post-ECMO arterial reconstruction.[57,58] Carotid reconstruction is not performed by all centers and may not always be possible. There are no data demonstrating an advantage with respect to long-term neurologic function in patients with as opposed to without carotid reconstruction. Long-term neurologic outcome may be more related to the condition of the patient at the time of initiation of ECMO, as well as to other factors related to their underlying condition (such as hypoxemia and adequacy of cerebral blood flow). Despite the lack of conclusive data, carotid reconstruction has advocates and is generally recommended if feasible. Direct cannulation of the ascending aorta is generally performed in patients who require emergent circulatory support in the immediate postoperative period. This approach enables the clinician to evaluate the mediastinum for evidence of tamponade and perform direct cardiac massage when needed. The principles of aortic cannulation used during cardiac surgery are applicable to ECMO patients. The site of cannulation should be above the sinotubular junction to avoid injury or distortion of the aortic valve, which may lead to valvular insufficiency. The cannula is secured with a purse-string suture and flexible tourniquet. It is important to direct the tip of the cannula away from the aortic valve while avoiding injury to the back wall of the aorta. Oversizing the cannula or advancing the cannula too far into the aorta may cause a mechanical obstruction to antegrade flow through the aortic arch and can contribute to difficulties in weaning ECMO support before decannulation. Femoral artery cannulation is useful in larger patients and in patients with compromised carotid blood flow. Either femoral artery may be cannulated under direct vision or using percutaneous Seldinger technique. The cannula is advanced so that the tip lies in the descending aorta. We advocate direct suture repair of the femoral artery at time of decannulation to limit subsequent limb morbidity related to vascular insufficiency. In some patients, it may be safer to sew a side graft onto the femoral artery and place the cannula into this side graft. This may be especially useful in patients with small femoral arteries in whom placement of an adequate size cannula would otherwise be hazardous. For example, a 5-mm side graft is large enough to allow insertion of a 14-mm cannula and an 8-mm side graft would easily accommodate a 22-mm cannula. This technique can be extremely valuable in selected cases and greatly reduces the risk of dissection of the femoral or iliac vessels during cannula insertion.

Venous cannulation is generally performed through the right internal jugular vein, either femoral vein, or the right atrial appendage. However, as with arterial cannulation, certain anatomic considerations may require the clinician to adopt unique venous cannulation strategies, such as is seen in patients who require support following superior cavopulmonary (Glenn) anastomosis.

The technique for VA-ECMO jugular venous cannulation involves placing a standard venous cannula into the internal jugular vein, and advancing the tip to the cavoatrial junction. Although this may be performed using the percutaneous Seldinger technique, we prefer to perform venous

cannulation under direct visualization to prevent unnecessary injury to the vascular structures in the neck and chest. We routinely perform jugular vein reconstruction at time of decannulation, though, admittedly, short- and long-term patency rates are poor. Alternatively, femoral venous cannulation may be performed through either femoral vein. We prefer the percutaneous Seldinger technique of cannulation when possible. The femoral venous cannula is advanced until the tip lies within the right atrium. Placement must be confirmed by chest radiography. Cannulation involving both femoral vessels in one leg or either femoral vessel in each leg is possible. Femoral vein reconstruction is generally not necessary after removing a venous cannula. The technique for right atrial cannulation is similar to that used in the operating room for CPB, utilizing a broad-based purse-string situated mostly on the right atrial appendage. A variety of cannulae may be used. Care must be taken to avoid injury to the sinoatrial node or the tricuspid valve during cannulation.

Aortic valve insufficiency and increased systemic arterial pressure may contribute to left ventricular distention, particularly in the setting of poor ventricular function. The subsequent increase in wall tension and myocardial oxygen demand will ultimately impede myocardial recovery. Improper carotid and aortic cannulation can exacerbate this process, by generating a flow jet that is directed toward the aortic valve. When necessary, decompression of the left ventricle may be accomplished in several ways. In the setting of a closed chest, left ventricular decompression may be accomplished by creating, or augmenting, an interatrial communication (Fig. 87-2). When present, a patent foramen ovale can be enlarged at the bedside by balloon septostomy under echocardiographic guidance. Alternatively, blade or balloon septostomy may be performed in the catheterization laboratory, even in the absence of a preexisting interatrial communication. Recently, Cheung et al.[59] have described an alternative method of left heart decompression, utilizing a percutaneous technique for inserting a vent into the left ventricle that is connected to the venous arm of the ECMO circuit. More options are available for decompressing the left heart in cases of an open chest. Since many of these patients are placed on ECMO in the operating room, a cannula can be placed directly into the left atrium and connected to the venous return of the ECMO circuit. This cannula can be placed through the left atrial appendage or in the space between the two right-sided pulmonary veins. Either site is easily accessible and readily visualized in an ICU setting if reexploration for any reason becomes necessary. Alternatively, a surgical atrial level communication by atrial septectomy can be performed, precluding the need for additional cannulae. Irrespective of the technique used, we believe it is important that left ventricular decompression is achieved soon after initiating ECMO support in patients with severely depressed left ventricular function. In addition to decreasing the likelihood of recovery of ventricular function, left ventricular distension may lead to increased left atrial pressure, causing fulminant pulmonary edema to rapidly ensue. In addition, the relative amount of coronary blood flow derived from the ECMO circuit (aortic or carotid cannula) or the lungs (through antegrade flow through the aortic valve) is dependent upon the amount of cardiac support provided by the ECMO circuit. At lower levels of support, the blood delivered to the coronary arteries is predominately derived from the left ventricle, whereas all coronary blood flow is derived from the ECMO circuit during periods of total cardiopulmonary support and the absence of left ventricular ejection.[60] Even at high ECMO flow rates, the coronaries preferentially receive blood supplied by the left ventricle blood. Effective left-sided decompression ensures that adequately oxygenated blood derived from the ECMO circuit will preferentially perfuse the coronaries in the setting of severely depressed lung function. This is an important consideration when weaning ECMO support. Moderate levels of mechanical ventilation must be continued during partial ECMO support and lung function must be adequate to wean ECMO support. Left ventricle decompression can be a source of air being introduced into the ECMO circuit and ECMO technicians need to be aware of this possibility. The decision to utilize left ventricular decompression is one that is dependent on the circumstances of the underlying pathology as well as the experience of the center. Excellent results can be achieved in centers where left ventricular decompression is used sparingly, if at all. In fact, left ventricle decompression in the setting of severe aortic insufficiency may simply set up a "recirculation" circuit and in these cases, ECMO may be contraindicated in lieu of aortic valve replacement or repair.

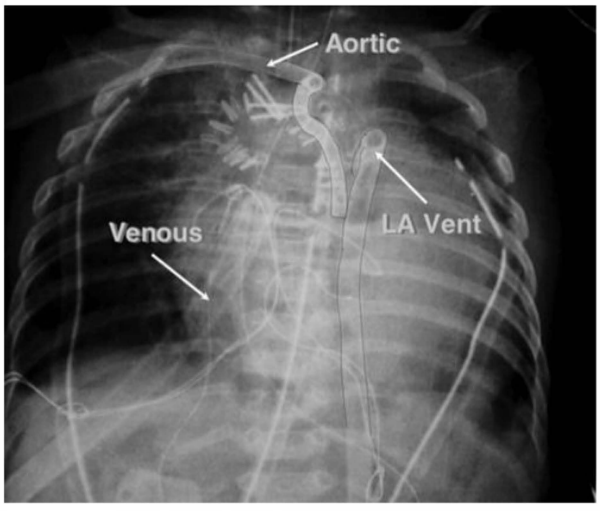



**FIGURE 87-2** Technique for left ventricular decompression.

## Management

Unlike the neonate with isolated respiratory failure, in whom ECMO flows and sweep gases are adjusted to maintain adequate oxygenation and ventilation, the infant or child on cardiac ECMO has cardiac insufficiency, often coupled with

respiratory insufficiency. The degree to which gas exchange is dependent on ECMO will obviously affect the management strategy. For the patient with isolated cardiac failure, ECMO flows are adjusted to ensure adequate end-organ blood flow. Clinical parameters, such as urine output and toe temperature, should be regularly scrutinized and ECMO flows adjusted to maintain adequate perfusion. Laboratory values, including arterial lactate and mixed venous oxygen saturations, are also important and should be followed serially. In general, flows of 100 to 150 mL/kg/min should be adequate to maintain homeostasis. Some circumstances, as in the case of an infant in whom the pulmonary and systemic circulations are in parallel (single ventricle with aortopulmonary shunt), may require considerably higher flows. It has been and continues to be our practice to keep aortopulmonary shunts open and utilize higher flows. Because of the non-pulsatile nature of generally available circuits, arterial waveform tracings may provide an indication of the degree of native cardiac contribution to systemic output. Lack of discernible pulse pressure indicates that the ECMO circuit is responsible for all the effective systemic blood flow. This circumstance can occur when the heart is completely bypassed, when there is "cardiac stun," or in the setting of cardiac failure. It is important to remember that coronary perfusion results from antegrade ejection of blood out the aortic valve, and it is only in the setting of nearly complete lack of cardiac output that coronary blood flow becomes dependent on the oxygen-rich blood returning via the arterial ECMO cannula. Bearing that in mind, it is important to ensure that whatever blood is being ejected out the left ventricle is well saturated, so that the heart does not suffer ongoing ischemia. Ventilator $F_{IO_2}$ should thus be maintained around 40 percent.

Serial echocardiograms can be helpful in gauging improvement in cardiac function, particularly in the setting of right ventricular failure where ventricular geometry and pressures can be assessed. Levels of brain natriuretic peptide (BNP) and cardiac troponin I can be followed serially as well. It is often necessary to reduce ECMO flows to allow cardiac filling in order to make a determination. During periods of flow reduction, systemic blood pressure and perfusion are monitored using the clinical parameters described above. Increases in arterial pulse pressure and perfusion indicate improving cardiac function and should encourage further weaning of ECMO flows. When flows have been sufficiently reduced, echocardiography is favorable, and perfusion is maintained on reasonable levels of inotropes, a trial off ECMO is warranted.

For the patient with combined cardiorespiratory failure, estimation of support needs and weaning preparedness are more complicated. In addition to ECMO flow rate, the sweep gas $F_{IO_2}$ and flow rate are important determinants of respiratory gas exchange. In many instances, restoration of adequate circulation with initiation of ECMO leads to rapid improvement in respiratory mechanics and gas exchange as interstitial and alveolar lung water is cleared. Likewise, restoration of normal arterial oxygen tensions and pH can precipitate significant improvement in cardiac function. In addition to the clinical and laboratory parameters previously discussed, regular monitoring of arterial blood gases is vital. Weaning involves gradual decreases in $F_{IO_2}$, sweep flow rate, and ECMO flow rate coupled with corresponding increases in mechanical ventilatory support. Once the patient can maintain physiologic values on reasonable ventilator settings and inotropes, a trial off ECMO is justified.

### Management of Systemic-to-Pulmonary Artery Shunts

One consideration for cardiac ECMO is how to handle systemic-to-pulmonary artery shunts, either in single-ventricle patients or in those with inadequate pulmonary blood flow. Our practice is to leave all shunts open, especially considering that the vast majority of our patients are peripherally cannulated through a cervical approach. Currently, we would support a patient with a modified Blalock-Taussig shunt on ECMO would be hypoxemia or evidence of a hyperactive pulmonary vascular bed. In both cases, we would employ venovenous ECMO (VV-ECMO) support with a single cannula placed in the internal jugular vein. In this case, the shunt is not affected by the presence of the ECMO cannula. In the case of a palliated HLHS patient, we again would favor VV-ECMO for low saturations. If a patient were in a state of low cardiac output after Norwood repair and required mechanical cardiac assist, we would use VA-ECMO via neck cannulation. However, we prefer the "Sano shunt" (a valveless conduit from the right ventricle to the pulmonary artery), which would not be affected by an arterial neck cannulation.

## VENOVENOUS EXTRACORPOREAL MEMBRANE OXYGENATION

Indications for VV-ECMO in the cardiac population may seem limited. In fact, as experience grows, more clinical applications become apparent. VV-ECMO has several potential advantages over VA-ECMO. First, in many instances only a single venous cannula is required and, obviously, no large-caliber arterial vessels are disrupted and potentially sacrificed. Second, physiologic pulsatile flow is maintained. Third, the pulmonary vascular bed is perfused with oxygen-rich blood. And last, the myocardium is perfused with oxygen-rich blood. The last two features deserve particular consideration as they apply to the cardiac population.

Pulmonary hypertension is a common comorbidity in the pediatric cardiac population.[61] Elevated pulmonary vascular resistance (PVR) and right ventricular dysfunction often lead to significant morbidity and even mortality in the perioperative period. In addition, infants with unrepaired cyanotic heart disease are at particular risk when they acquire common viral respiratory illnesses.[61–64] We have found VV-ECMO to be the ideal mechanical support mode in these settings to improve oxygenation, correct of respiratory acidosis, and reduce PVR. Clinically, the result is increased

pulmonary blood flow, decreased right ventricular strain, better left-sided filling, enhanced myocardial oxygenation, and improved cardiac output. We consistently note rapid decreases in inotropic requirements following the institution of VV-ECMO.

Imamura and associates at Arkansas Children's Hospital report a similar experience in 10 patients placed on VV-ECMO for support in the setting of acute viral pneumonia and another 8 patients with inadequate pulmonary blood flow.[61] In each of these two groups, VV-ECMO served as a bridge to recovery or surgical intervention. Survival to discharge was 95 percent.

## Implementation and Cannulation

Placing a patient on VV-ECMO is less complicated than placing one on VA-ECMO. Options for cannulation strategy with VV-ECMO, as opposed to VA-ECMO, are also greater, in that specialized bicaval cannulae are available that allow simultaneous venous drainage from both the superior and inferior vena cava and reinfusion of blood into the atrium through a third aperture. These cannula are currently available for larger patients (though shortly a wire-reinforced model suitable for neonates under 5 kg will be available), and mitigate recirculation and improve venous drainage. The cannula is inserted through the right internal jugular vein and advanced using echocardiographic guidance, so that the tip lies in or near the inferior vena cava and the side-port is within the atrium.

## Management

The management of VV-ECMO differs from that of VA-ECMO in many ways. Cardiac output is not supported in any way other than the improvement in native ventricular function discussed above. As such, adjustments in ECMO flow rates do not directly affect blood pressure and perfusion. Mechanical ventilation is usually maintained using a lung-protective strategy to minimize airway trauma and optimize lung repair. In addition, adequate lung inflation is necessary to avoid elevations in PVR related to interalveolar capillary collapse (Fig. 87-3). In those patients supported due to inadequate pulmonary blood flow, surgical creation of a palliative shunt or full repair can be accomplished when the patient's physiologic parameters have normalized, making the child a better candidate for anesthesia and/or CPB.

Functionally, pump flow rate, sweep gas flow, and $F_{IO_2}$ are adjusted to achieve the desired oxygen saturations and arterial blood gas parameters. Weaning is attempted when chest x-ray findings and pulmonary mechanics indicate improvement in respiratory function or when PVR and right ventricular function have improved. Sweep flow and $F_{IO}$ are weaned and mechanical ventilator settings increased accordingly. When sweep gas settings are minimized and ventilator settings are reasonable, removal of the patient from VV-ECMO can be tried by capping the gas source. Initiation of a pulmonary vasodilator (iNO, phosphodiesterase inhibitor V) in patients with pulmonary hypertension may facilitate the transition from mechanical support.

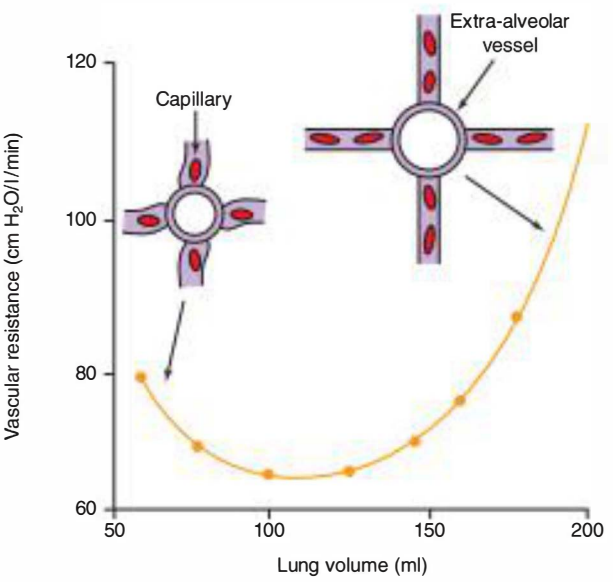



**FIGURE 87-3** Pulmonary vascular resistance in relation to lung volume. Pulmonary vascular resistance is at its nadir when the lung is at functional residual capacity (FRC). In settings of either atelectasis or overdistention, pulmonary vascular resistance increases.

## Anticoagulation

During open cardiac surgical procedures, the patient's entire blood volume is exposed to both the bypass circuit and the surgical wound, both of which stimulate activation of all blood elements involved in the inflammatory cascade.[65] Patients placed on ECMO following cardiac surgery continue to be exposed to a large biomaterial surface with its attendant complications. Over time, equilibrium can eventually be established between the activation and neutralization of inflammatory blood elements and this equilibrium is essential for continuation of ELCS. Most of our understanding of the activation of blood components comes from experience with intraoperative CPB, although there is a growing body of literature specific to ECMO.

Once blood contacts the ECMO circuit, plasma proteins are instantly adsorbed onto all nonendothelial surfaces.[66–68] These proteins are tightly packed, irreversibly bound, and stationary.[68] Fibrinogen is adsorbed by the hydrophobic surface of these biomaterials.[66] This surface will eventually stimulate clot formation and activate blood elements, including five plasma protein systems (contact system, intrinsic coagulation pathway, extrinsic coagulation pathway, fibrinolysis, and complement) and five blood cell types

(platelets, endothelial cells, neutrophils, monocytes, and lymphocytes).

Platelets adhere to the ECMO circuit and become activated, causing them to degranulate and release substances that in turn activate even more platelets.[69] Thrombin is generated by the coordination of the plasma protein systems and further activates platelets. Platelets change shape by extending pseudopods and begin to express GPIIb/IIIA receptors, which bind platelets, using fibrinogen as a bridge.[70] Adherent platelets will detach and fragment, leading to a decrease in the number of normal platelets in the circulating pool.[71] The activation of the coagulation system is not limited to activity within the ECMO circuit, as patients may develop systemic disseminated intravascular coagulation (DIC).

In addition to the impact of the circuit, the exposure of circulating monocytes to the surgical wound will potentiate the activation of the coagulation system. Monocytes will elaborate tissue factor and continue the activation of the intrinsic and extrinsic coagulation pathways.[70] Although this is usually of a self-limited nature in open cardiac procedures, it can have a protracted effect in patients who require transthoracic cannulation for ECMO.

The activation of the coagulation system from exposure to the ECMO circuit and the surgical wound makes anticoagulation a necessity. However, it can be exceedingly difficult to achieve the delicate balance between appropriate anticoagulation and hemorrhage control in postoperative cardiac surgical patients. The ideal anticoagulant would inhibit platelet activation and aggregation as well as activation of the coagulation cascade but would maintain enough procoagulant properties to allow for coagulation at the surgical site. Traditionally, heparin has been the most commonly used anticoagulant for all forms of ECLS, although it is far from an ideal agent.

Heparin inhibits thrombin and factor Xa generation, requiring normal levels of circulating thrombin and accelerating its action approximately 1000 times. Heparin's effects can be blocked with protamine, enhancing its attractiveness. However, heparin does not have any effect on platelet activation and does not inhibit the generation of thrombin merely its activity. Large doses of heparin are routinely required during ECMO, mainly due to inactivation of the heparin molecule by mechanisms in both blood and the circuit, which eliminate more than half of the administered heparin.[72] Of additional growing concern is the recent increase in awareness of allergic reactions to heparin, manifesting as heparin-induced thrombocytopenia (HIT).

The majority of ECMO centers continue to follow *activated clotting times* (ACT) to titrate heparin therapy. ACT is a crude measure of the effect of heparin on whole blood, but its ease of use in point-of-care testing makes it the preferred method. Prior to cannulation, patients not already anticoagulated require an initial heparin bolus (usually 75 to 100 U/kg), which is followed by a continuous infusion to maintain the ACT between 180 and 220s. Postoperative patients will usually require the lower end of the range and may not receive much heparin at all in the first 24 to 48 h in order to promote hemostasis at the surgical site. Other agents and techniques may be on the horizon, including a reduction in circuit thrombogenicity and the development of alternative selective anticoagulants.

Argatroban is a potent, reversible, direct thrombin inhibitor that has been suggested as an alternative therapy in patients who develop heparin sensitivity. In laboratory experiments, Argatroban is associated with absence of clot initiation and a decrease in thrombin generation, raising its potential as a heparin alternative.[73] Its use has been reported to facilitate CPB in a heparin-sensitized infant undergoing tricuspid valve removal secondary to bacterial endocarditis.[74] Recent reports from the Oregon Health Sciences University have noted the successful use of argatroban in ECMO patients with probable HIT.[75]

Nafamostat mesylate is a broad-spectrum protease inhibitor that suppresses activation of contact proteins during ECMO.[76] It has been shown to reduce heparin requirements and resulted in a shorter ACT in the patient than the ECMO circuit.[77] Use of this agent during CPB has been shown to reduce postoperative blood loss.[78] A 1997 study by Nagaya and colleagues used nafamostat in 12 newborns that had hemorrhagic complications before or during ECMO.[77] The ACT of the blood delivered to the patient was reduced by 27s compared to the circuit ACT and was associated with control of bleeding in 66 percent of the patients.

As previously discussed, heparin-bonded circuits have been developed using covalent (Cardmeda systems, described above) and ionic bonding (Duraflo II, Baxter) techniques. Heparin bound to the surface exerts an antithrombin-mediated inhibition of thrombin and factor Xa. The thrombin–antithrombin complexes bind to the surface without functionally blocking the activity of the immobilized heparin and serve to decrease exogenous heparin requirements.[69] A laboratory investigation of heparin-coated and uncoated systems was performed by Urlesberger and coworkers.[79] They found that coagulation system activation and D-dimer formation were significantly delayed in the heparin-coated group. After 6 h, no differences between the groups were detected, and after 24 h, markers had returned to near baseline values. The authors concluded that these circuits may provide only limited advantages in long-term ECMO use. However, they do offer benefits to those patients with a high bleeding risk, as they allow for less systemic heparinization.

Protease inhibitors, such as aminocaproic acid (Amicar), function primarily through inhibition of the fibrinolytic system and to a smaller extent by inhibition of the coagulation system. They have been shown to significantly reduce the requirements for blood products during CPB. A 1993 study reported a decrease in the incidence of intracranial hemorrhage and other hemorrhagic complications in patients on ECMO treated with Amicar.[80] In addition, Amicar's use is widely reported in the cardiac ECMO literature as an adjunct for postoperative patients with significant postoperative bleeding.[81] The caveat, however, is that Amicar will likely shorten the life expectancy of the ECMO circuit.

## FEEDING

Critically ill patients on ECMO typically have significant nutritional requirements. In fact, neonates on ECMO have demonstrated some of the highest rates of protein catabolism reported.[82] Postoperative cardiac surgical patients have the added burden of wound healing, which further increases their nutritional needs. Therefore, provision of adequate nutritional support in this population must be predicated on a clear understanding of these patients' perturbed metabolic state. Current guidelines published by the American Society for Parenteral and Enteral Nutrition recommended that nutritional support, consisting of 100 to 120 kcal/kg/day and protein of 3 g/kg/d), be initiated as soon as possible for neonates on ECMO.[83] Parenteral nutrition has traditionally been the primary source of calories for patients on cardiac ECMO because of the risk of impaired splanchnic perfusion and bacterial translocation in the setting of cardiopulmonary failure. However, enteral feedings have been shown to be beneficial by maintaining gut mucosal integrity, improving gastrointestinal immunologic function, and reducing septic morbidity.[84–88] The current guidelines support initiating enteral feeding once the patient has stabilized and gastrointestinal function is thought to be normal. Parenteral nutrition should be continued until the enteral feeds have been uptitrated to goal. Although there are no studies focusing exclusively on cardiac ECMO patients, a recent large retrospective study in neonates on ECMO demonstrated tolerance of enteral feeding without serious adverse events.[84] In that study, 67 of 77 VA-ECMO patients received enteral feedings. Dopamine infusion was administered to 80 percent of these patients, with a median dose of 7 μg/kg/min and a maximum dose of 20 μg/kg/min. Three patients were on both dopamine and dobutamine, and four patients received both dopamine and epinephrine. The patients on inotropic support did not have an increase in the rate of retained feedings or adverse outcomes. Another series retrospectively compared 13 patients on ECMO receiving total enteral nutrition to 14 matched patients receiving parenteral nutrition. These authors found that enteral nutrition was well tolerated without complications.[89] Administration of intravenous lipids in association with parenteral hyperalimentation for patients on ECMO raises particular concerns related to their effect on the extracorporeal circuit. In an in vitro analysis, a fat emulsion was infused into ECMO circuits at a rate of 3 mL/h.[88] All circuits showed layering (separation of fat emulsion from blood) and agglutination at 24 h. Adhesion of the emulsion to the circuit was evident in all samples. This study, along with anecdotal experience at many other ECMO centers, suggests that fat emulsions should be infused through separate intravenous sites whenever possible.

### Immune Prophylaxis

Some centers routinely utilize immunosuppressive agents prior to initiation of ECMO and during subsequent circuit changes. This practice has intuitive appeal due to the inflammatory cascade that is triggered upon exposure of the patient's blood components to the foreign surfaces of the ECMO circuit. Griffin and colleagues recently published a randomized, double-blind, controlled trial of dexamethasone versus placebo in infants placed on ECMO for respiratory failure.[90] They randomized 59 infants to either group and noted significant improvement in lung injury scores in the dexamethasone arm versus the placebo arm on day 3 of ECMO. However, they did not find a significant difference in outcome between the two groups, as the mean ECMO duration was 143.5 hours in the dexamethasone group and 160 hours in the placebo group. Therefore, although steroids may ameliorate some of the inflammatory response, their effect on long-term outcome is less certain.

Hypothermia is routinely utilized in CPB and appears to play a role in modulation of the immune response to the CPB circuit. Recent laboratory investigations have noted the role of hypothermia in altering the activities of neutrophils, which have been shown to be associated with decreased endothelial adherence and decreased release of L-selectin from the bone marrow in the setting of hypothermia.[91–93] These data are intriguing and suggest a new area of focus as investigators pursue ways to minimize the immunologic response to ECMO.

## EQUIPMENT

The typical ECMO circuit comprises three main parts: a pump, an oxygenator, and a heat exchanger. Additional components include the tubing to transport the blood and other pieces of equipment that serve as monitoring devices and ensure safe operation of the ECMO circuit. Regardless of the type of ECMO utilized, the basic principles of the circuit remain the same (Fig. 87-4). Deoxygenated blood is removed from the patient, accelerated in a pump, oxygenated, heated, and then returned to the patient. Tubing size, oxygenator volume, and requisite flow rates will differ based on patient size; these variables have hematologic and immunologic implications for the patient. Platelet consumption will increase in proportion to the surface area of the membrane lung (within the oxygenator), activating the immune response.[94] Neonatal circuits may require the equivalent of twice the patient's circulating blood volume to prime, while in an adult the circuit priming volume may represent only half the circulating blood volume.[95,96]

The following sections discuss details related to pumps, oxygenators, heat exchangers, tubing, and safety and monitoring devices.

### Pumps

First developed by Gibbon, the standard roller pump (Fig. 87-5) has been the device most widely used for ECMO over the past 30 years. Its popularity is based on the fact that



**FIGURE 87-4** ECMO circuit.

it is a relatively inexpensive, predictable device with a simple design that responds well to servo-control. Blood flow is generated by the compression of the tubing that forces blood forward ahead of the moving roller. As one end of the roller completes its compressive phase, the other end is just beginning. Compression is carefully adjusted to be just nonocclusive in order to generate forward flow and minimize hemolysis and tubing wear.[97] However, this device does have the following significant limitations. It is dependent upon gravity drainage from the venous system to maintain adequate inflow pressure. It requires continuous servoregulation and pressure monitoring to prevent the development of excessively negative or positive pressure within the circuit. Excessive negative circuit pressure may result in cavitation, causing air to be drawn out of solution. Furthermore, excessive negative pressure may result in hemolysis or damage to venous and/or atrial structures near the site of cannulation.[94] An in-line bladder is generally utilized to assist in monitoring and servoregulation of the ECMO circuit to prevent excessive negative pressure. Excessively elevated circuit pressure may result in circuit rupture. When the system is compromised, the roller pump has the potential to pump a large volume of air, leading to massive air embolism. Long-term use of the roller pump may cause spallation of the tubing within the pump housing, potentially resulting in embolization of particulate matter or even complete circuit rupture due to repetitive occlusions.

Owing to the concerns with roller pumps, attention has been refocused on centrifugal pumps. These pumps (Fig. 87-6) use rotating cones activated by a forced vortex pumping action. These pumps cause less trauma to blood elements, although fibrin deposits in the pumping chamber can limit their useful life to 5 to 7 days.[98] Unlike the

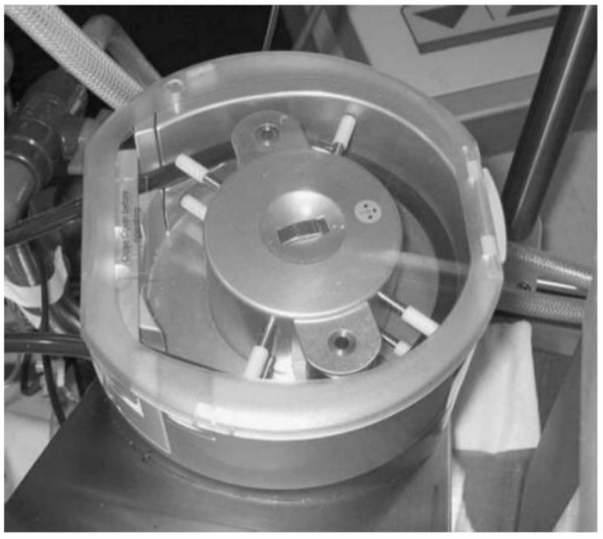


**FIGURE 87-5** Roller pump.

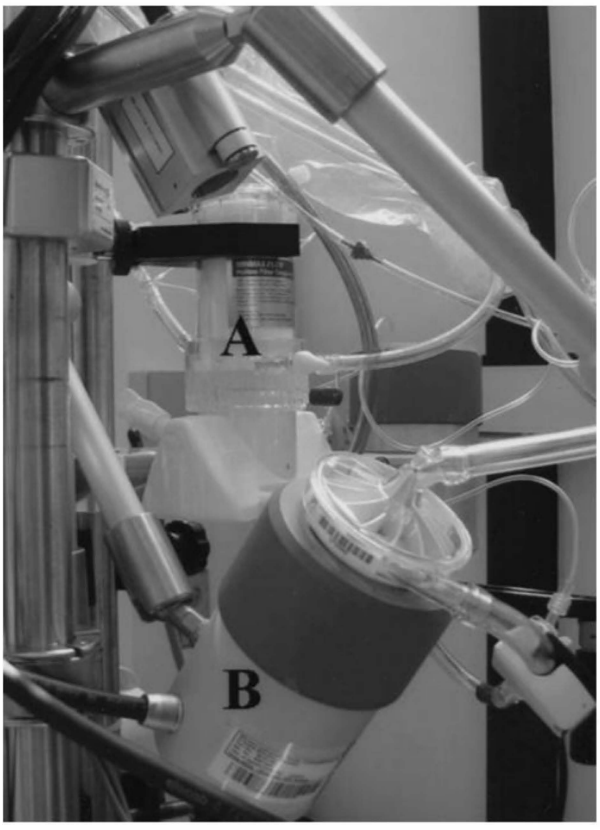



**FIGURE 87-6** **A.** Hollow-fiber oxygenator. **B.** Centrifugal pump.

case with roller pumps, inflow here is gravity-independent, allowing the pumps to be placed at any height. The pump is sensitive to preload and afterload, either of which will affect pump flow. Unlike roller pumps, centrifugal pumps will come to a stop when they have entrained a large amount of air. Centrifugal pumps, however, can generate large negative pressures, which may lead to cavitation and hemolysis. The development of newer hollow-fiber oxygenators such as the Quadrox, which have less resistance, interface much better with centrifugal pumps. An ECMO circuit consisting of a centrifugal pump coupled with a hollow-fiber oxygenator is rapidly becoming the preference of larger ECMO centers.[28]

## Oxygenators

The artificial oxygenator functions like a lung, adding oxygen to the circulating blood and removing carbon dioxide. An ideal extracorporeal lung should be noncompliant, so that blood volume remains constant, thus minimizing the risk of thrombosis and hemolysis.[94] In modern oxygenators, blood flows into a manifold region, from which it disperses to the microporous fibers of a *hollow-fiber oxygenator*. Oxygenated gas flows through the device in countercurrent to the flow of blood. Oxygen diffuses across the membrane into the blood and carbon dioxide is eliminated. Because of the high carbon dioxide diffusing capacity of these devices, in some instances carbon dioxide may actually need to be added to the gas mixture in order to normalize the patient's arterial blood gas. Oxygen does not diffuse as readily and is limited by the time period that the hemoglobin molecule is in transit through the oxygenator. As a result, oxygenators are limited in their oxygenating capacity based on the pump flow rate and are differentiated by the threshold rate above which the oxygenator is no longer able to increase the saturation of venous blood from 70 to 95 percent.[99]

Oxygenators are susceptible to clot formation, collapse, edema, hemorrhage, and thrombosis.[99,100] Ventilation/perfusion mismatching can ensue. Water, plasma, and blood may collect in the gas phase of the oxygenator and decrease the rate of carbon dioxide exchange. Accordingly, $P_{CO_2}$ can be a sensitive indicator of edema accumulation, which results in a decrease in the functional gas-exchange surface.[94]

Hollow-fiber oxygenators have low internal resistance, which allows them to be coupled with centrifugal pumps. These devices utilize microporous capillaries, around which blood flows and contacts the ventilatory gas. Advantages include low resistance and low priming volumes (as low as 250 mL). Disadvantages include a propensity for plasma leakage (exacerbated by intralipid use) and undesired ultrafiltration.[94] New-generation hollow-fiber oxygenators, such as the Quadrox®, appear to be less susceptible to these shortcomings.[102–108] Motomura and colleagues have achieved stable gas performance with minimal plasma leakage over a 2-week period of use.[108] With continued improvements in technology, hollow-fiber oxygenators are increasingly be used with ECMO and are encouraging a shift toward centrifugal pumps.

## Heat Exchangers

The *heat exchanger* is the last part of the circuit through which the blood passes en route back to the patient. Structurally heat exchangers are composed of silicone-coated stainless steel tubes that allow warm water to flow outside the ECMO circuit in a countercurrent fashion. Blood is heated as it flows vertically from the upper to lower portion, permitting air bubbles to be trapped in the upper section.[100] Heat exchangers are particularly important in the management of neonatal patients due to their propensity for temperature instability. Device failure occurs in some 1 to 2 percent of ECMO cases.[109] Most commonly, failure is due to the leakage of water from the connectors at the top and bottom of the device. Leakage of blood is uncommon and, because of the higher pressure in the ECMO circuit, leakage of water into the blood phase is even less common.[100]

## Tubing

Circuit tubing has improved significantly since the advent of ECMO 30 years ago. Most of the circuit consists of polyvinyl chloride tubing, a readily available and relatively inexpensive product. One potential disadvantage with polyvinyl chloride tubing has been the release of the plasticizer di(2-ethylhexyl) phthalate (DEHP), which animal studies show may result in decreased fertility, reduced sperm production in males, and ovarian dys-function.[110–112] However, a 2004 study by Khodayar and associates found that adolescents exposed to DEHP as neonates on ECMO showed no adverse effects on their physical growth, maturation, or liver, thyroid, renal, and gonadal function.[113]

Polyvinyl chloride tubing, however, is not durable enough for the "raceway" the portion of the circuit passing through the roller pump. Instead, most ECMO centers currently utilize Super Tygon tubing, S-65 HL, in the raceway, as it is more resistant to rupture and has been shown to minimize spallation (fragmentation and release of microparticles from plastic). Heparin-bonded circuits have been developed in an effort to reduce thrombotic complications (see the discussion of anticoagulation, below). The Carmeda Bioactive Surface (CBAS; Carmeda, Stockholm, Sweden) is a covalent endpoint bonding coating that attaches the heparin molecule to the plastic while the antithrombin-binding site remains exposed.[114] Systemic heparin requirements are significantly reduced in heparin-bonded circuits versus nonheparin-bonded circuits.[115,116] In addition, the Carmeda coating has been shown to reduce DEHP leakage from polyvinyl chloride tubing.[117]

## Cannulae

Appropriate choice of cannulae is critically important to maximize ECMO efficiency and limit hemolysis. The size of cannulae used is based on patient body weight and the size of the vessels to be cannulated. Several types of cannulae are

currently used for ECMO. Each type of cannula is associated with distinct advantages and disadvantages; there is no perfect cannula. Arterial cannulae (VA-ECMO) are available in sizes ranging from 8F to greater than 23F to accommodate vessels ranging from even the smallest carotid artery to an adult ascending aorta. Because they are essentially incompressible and resist kinking, wire-reinforced cannulae are especially well suited for ECMO. Smaller arterial cannulae are often packaged with a specialized stylet to facilitate cannulation of small vessels. Venous cannulae used for VA-ECMO contain multiple fenestrations to improve venous return to the circuit. Some cannulae feature a malleable distal tip that enables the cannula to be tailored to the unique geometry of the heart during chest cannulation. Larger diameter, dual-lumen cannulae are designed to allow VV-ECMO support through a single cannulation site.

## Safety and Monitoring Devices

### BLADDER RESERVOIR

A recent survey by Lawson and coworkers found that 92 percent of American ECMO centers utilize a bladder reservoir (Fig. 87-7) in the ECMO circuit.[101] The bladder is situated just proximal to the pump and serves a variety of functions. Aspiration ports associated with the bladder allow for the removal of any air that may have inadvertently been introduced into the circuit. Likewise, the bladder provides access to the circuit whereby medications, infusions, blood products, and volume may be administered. Last, prebladder pressures are routinely measured via a transducer and provide a quantifiable estimate of the venous return pressure (volume). Servoregulated pumps will decrease and even shut off flow as the bladder pressure approaches or falls below a critical value.

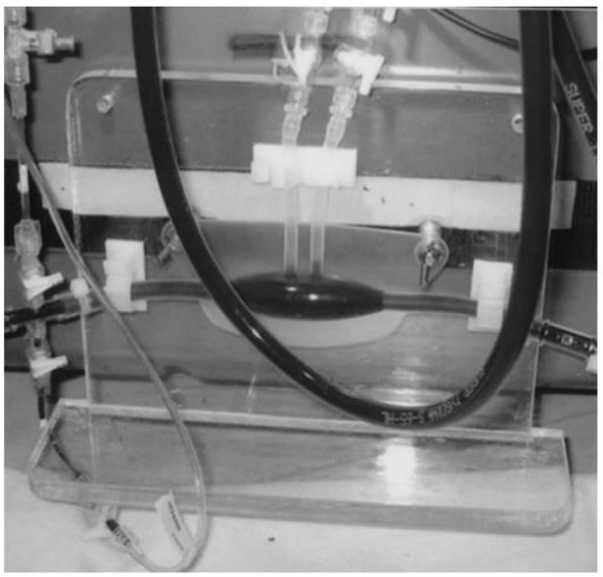


FIGURE 87-7 Bladder reservoir.

A small volume bladder is frequently incapable of handling large flow rates and pressure (volume) fluctuations associated with older patients. In this situation, the ECMO circuit may incorporate a parallel segment of tubing to allow blood to bypass the bladder and be diverted directly into the pump.

### PRESSURE TRANSDUCERS

Circuit pressures are usually monitored prebladder ("inflow") and between pump and patient ("line").[118] Pre- and postoxygenator pressures are usually monitored in an effort to detect distal circuit (especially within the oxygenator) thrombosis and/or tubing kinking, both of which could lead to catastrophic circuit rupture if uncorrected.[94] Isolated increases in preoxygenator pressure in the setting of a normal postoxygenator pressure indicates thrombosis within the oxygenator, and is an early harbinger of oxygenator failure. Generally speaking, a rising pressure gradient across an oxygenator predicts oxygenator failure. There is a greater risk of circuit disruption when preoxygenator pressures are above 400 mm Hg, probable when they are above 500 mm Hg, and imminent when the pressure exceeds 600 mm Hg.[94]

### BUBBLE DETECTORS

Bubble detectors are an added safety precaution, and are usually incorporated into the circuit near the site of patient inflow.[101] Although the bladder, oxygenator, and heat exchanger all scavenge large bubbles, making air-embolism unlikely, bubble detectors typically have automatic shutoff switches and serve as a last check before blood returns to the patient.[119] Once the circuit shuts down, the air bubbles rise to the top of the heat exchanger, where they can be removed through distal circuit aspiration ports.

### THE BRIDGE

A segment of tubing, referred to as "the bridge," usually connects the arterial and venous limbs of the ECMO circuit. Its main function is to allow the patient to be temporarily removed from the ECMO circuit during a trial off support or during an emergency. In such an instance, the bridge is unclamped and the proximal arterial and venous lines are clamped. The patient is thereby excluded from the circuit and blood can continue to circulate within the ECMO circuit. During normal ECMO operation, the bridge remains clamped but must be "flashed" every 20 to 30 minutes to prevent stagnation and possible thrombosis within that segment. Flashing of the bridge has been associated with an initial decrease and then a secondary increase in mean arterial pressure and mean left carotid artery blood flow.[120] Cerebral oxygen delivery is decreased because of this arteriovenous shunt, which may lead to an increase in cerebral oxygen extraction and vasodilatation and eventually an increase in cerebral blood volume and excess cerebral oxygen delivery.[121]

Reperfusion injury, with free-radical formation, could occur in this setting and potentiate or cause cerebral injury.

Experimental work done by Totopally et al. suggests that leaving the bridge open throughout normal ECMO support reduces fluctuations in systemic arterial pressure caused by flashing the bridge. However, this is not routine practice.[122]

## CONCLUSIONS

Exciting advances in extracorporeal membrane support equipment, techniques, and experience have led to the expansion of its use in the pediatric cardiac population. Consideration of earlier initiation of support is warranted based on outcomes reported in the literature as well as the theoretical advantage of avoiding multiorgan dysfunction associated with LCOS. Furthermore, improved myocardial repair and recovery is possible when demands on the failing heart are decreased. Nevertheless, thoughtful, realistic consideration of the myriad clinical and programmatic issues associated with cardiac ECMO must be pursued on an individual case basis to ensure its judicious use and to avoid application of futile or heroic care.

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## EXTRACORPOREAL MEMBRANE OXYGENATION IN PEDIATRIC CARDIAC CARE BOARD REVIEW QUESTIONS (CHAPTER 87)

1. Which is not a risk factor for mortality on VA-ECMO?
   A. Age less than 1 month
   B. Male gender
   C. Duration of mechanical ventilation prior to initiation of support
   D. Single ventricle physiology
   E. Hepatic dysfunction

2. Which is true for VA-ECMO as bridge to transplantation?
   A. Mortality approaches 50 percent.
   B. There is lower survival compared to recipients not requiring VA-ECMO.
   C. Overall survival to discharge is 70 percent combining transplant recipients and patients bridged to recovery.
   D. Pre-ECMO cardiac arrest is not associated with poorer outcome.
   E. Mortality with the Berlin Heart EXCOR is about 10 percent.

3. Which is correct regarding surgical technique for ECMO?
   A. The right common carotid artery is the preferred site for arterial cannulation in neonates and infants.
   B. The tip of the arterial cannula should lie in the ascending aorta.
   C. Carotid reconstruction has been shown to improve long-term neurologic function.
   D. If the femoral artery is used, the tip of the cannula should lie in the iliac artery.
   E. The tip of the venous cannula should lie well into the right atrium.

4. Which is true for VV-ECMO?
   A. Two cannulae are preferred.
   B. Physiologic pulsatile flow is eliminated.
   C. The pulmonary vascular bed is perfused with oxygen-rich blood.
   D. The myocardium can be at risk for poor oxygenation.
   E. The lungs are collapsed.

5. Which is true regarding anticoagulation for ECMO?
   A. Heparin inhibits the generation of thrombin.
   B. The ACT is maintained between 250 and 300 s.
   C. Heparin-bonded circuits delay activation of the coagulation system for up to 48 h.
   D. Amicar decreases the incidence of intracranial hemorrhage.
   E. Nafamostat does not reduce heparin requirements.

## ANSWERS

1. **Answer: D.** Single ventricle physiology is not a risk factor for mortality on VA-ECMO. Age less than 1 month, male gender, duration of mechanical ventilation prior to initiation of support, renal dysfunction, and hepatic dysfunction are all risk factors.
2. **Answer: A.** Mortality is 40 to 50 percent for VA-ECMO as a bridge to transplantation. Survival is equivalent to patients not requiring VA-ECMO prior to transplantation. Overall survival to discharge is 50 percent combining transplant recipients and patients bridged to recovery. Pre-ECMO cardiac arrest is associated with poorer outcome. Mortality with the Berlin Heart EXCOR is about 25 percent.
3. **Answer: A.** The right common carotid artery is the preferred site for arterial cannulation in neonates and infants. The tip of the arterial cannula should lie at the base of the innominate artery. Carotid reconstruction has not been shown to improve long-term neurologic function. If the femoral artery is used, the tip of the cannula should lie in the descending aorta. The tip of the venous cannula should lie at the cavoatrial junction.
4. **Answer: C.** The pulmonary vascular bed is perfused with oxygen-rich blood. A single venous cannula is often all that is required. Physiologic pulsatile flow is maintained, and the myocardium is also perfused with oxygen-rich blood. The lungs are ventilated to avoid elevations in pulmonary vascular resistance.
5. **Answer: D.** Amicar decreases the incidence of intracranial hemorrhage and other hemorrhage complications. Heparin does not inhibit the generation of thrombin. The ACT is maintained between 180 and 220 s. Heparin-bonded circuits do not delay activation of the coagulation system past 24 h. Nafamostat has been shown to reduce heparin requirements.

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88

# Ventricular Assist Devices in Children

*Kristen Nelson*
*Luca A. Vricella*

**KEY CONCEPTS**

- The parallel growth of pediatric cardiac surgery and ventricular assist device (VAD) technology has led to the development of mechanical support specifically tailored to the management of pediatric heart failure. Pediatric VADs are used for heart failure refractory to conventional medical therapy and act as bridges most often to transplantation, but may also act as a bridge to recovery. Each one of the numerous devices currently available has specific advantages, but device selection must be individualized to the patient's particular anatomy and clinical circumstances. A large NIH trial is currently ongoing to further develop continuous flow VADs for the smaller pediatric population, due to the promising results seen in adult continuous flow device studies. Anticoagulation and infection prophylaxis remain major concerns in the management of pediatric patients undergoing VAD placement, but protocolized management will allow us to further study the complex interactions between inflammation, immunity and use of VADs in the pediatric population.

## INTRODUCTION

Ventricular assist devices (VADs) can be invaluable tools for the management of end-stage heart failure in children. While development of such devices in adults has grown significantly since the 1960s and has led to several generations of VAD enhancements, the development of such devices in children has not grown at the same rate. This slower evolution has been due to a number of factors, such as the inherent differences in anatomic and physiologic parameters in children, especially in patients with congenital heart disease involving a variety of defects, as well as developmental changes in the coagulation system. The last 10 years, however, have witnessed an increased attention for VAD development and use in the pediatric population. This increase is due to the fact that while heart transplantation remains the ultimate therapy for children with advanced heart failure, the number of pediatric heart transplants has not increased over the past 10 years to meet the increase in demand. In fact, of all patients on the waiting list for solid-organ transplantation in the United Sates, children listed for heart transplantation face the highest waiting list mortality regardless of age.[1,2] Therapeutic options, therefore, become limited at the point of end-stage heart failure, particularly with pediatric heart transplant wait times often exceeding 4 to 6 months, especially for patients 5 years of age and younger. Due to these factors, it is anticipated that more children with both congenital heart disease and cardiomyopathy-associated heart failure will require long-term VAD support in the coming decade as a bridge to transplantation or recovery.

Historically, extracorporeal membrane oxygenation (ECMO) was the only readily accessible form of mechanical assist for both long and short-term (i.e., postcardiotomy) support. Long-term use of ECMO was limited by complications and often lack of rehabilitation of patients in preparation for transplantation. There were limited options for other long-term assist devices until 2000, when the Berlin Heart EXCOR pulsatile VAD was first utilized in a US pediatric patient under compassionate use approval by the FDA. Over the ensuing 10 years, the Investigational Device Exemption (IDE) study was conducted by Berlin Heart, Inc., eventually leading to FDA approval in late 2011.[3,4] Over this time, there have been advancements in the design of such devices, which permit their placement in neonates and older children in univentricular or biventricular support configuration. There is also a wealth of research currently underway for the development and evaluation of new VADs to further

enhance outcomes for pediatric patients requiring these devices as part of the PumpKIN (Pumps for Kids, Infants and Neonates) trial sponsored by the NIH NHLBI.

While pediatric indications for mechanical circulatory support are often very different from those of the adult population, the same goal of bridging the failing heart to recovery or transplant may be accomplished. Successful myocardial recovery may occur with temporary mechanical assist for myocarditis, failure to wean from bypass (i.e., postcardiotomy) and heart transplant graft failure, through the use of ECMO, Tandem Heart or Rotaflow, to name a few examples, with ECMO remaining the most commonly used short-term device at present. More long-term mechanical support for heart failure due to cardiomyopathy, some cases of myocarditis or various congenital heart lesions often requires a VAD such as Berlin Heart EXCOR for infants and children and Thoratec HeartMate II or HeartWare for older children and adolescents. Most commonly, long-term pediatric VADs are placed with the intent of successful bridging to transplantation, although recovery has been reported.[5–8] The results of several studies indicate a definite benefit in this patient population, with a recent study revealing significantly higher survival rates with the Berlin Heart EXCOR device than with ECMO for pediatric patients with heart failure. However, VADs can be associated with significant morbidity and mortality, most commonly due to infection, hemorrhage and/or thromboembolism resulting in stroke.[2]

Mechanical support for failing pediatric hearts must be customized to the individual's need, size, anatomy and physiology. Certainly, in children from neonatal age to adolescence, one size does not fit all. In the United States, the initial reports of mechanical pediatric cardiac support entailed utilization of devices initially intended for the adult patient population. Therefore, many of these devices were too large to accommodate the specific requirements of the small child and ECMO was the mainstay of circulatory assist in this particular group. Fortunately, with the development of the EXCOR Berlin Heart VAD and FDA approval for study in the United States, it has become the most commonly used VAD for pediatric patients less than or equal to body surface area (BSA) 1.5 $m^2$. (Of note, Berlin Heart EXCOR has pumps available for adult size patients, but is not FDA approved for use above 1.5 $m^2$ at this time.) For older patients requiring VAD support, Heartmate II and Heartware have become viable options and allow patients to resume normal daily activities, such as participation in school.

Pediatric patients in acute need of ventricular assistance often differ from those who present with more chronic heart failure that has progressed despite maximal medical therapy. Indeed, the decision as to which device to use should be based on the indication and prognosis (Fig. 88-1). A patient who cannot be weaned from cardiopulmonary bypass might only need ventricular support for a few days while the myocardium recovers, while another patient with end-stage heart failure might require a VAD designed for longer use that is both portable and durable in anticipation of a lengthy wait on a heart transplant list.

New devices are constantly being developed, and adult VADs will continue to be adapted to the pediatric patient population. As the technology evolves and becomes more readily available, VADs will likely become a mainstay of the management of pediatric heart failure in both the acute and chronic settings.

## PATHOPHYSIOLOGY

Pediatric heart failure severe enough to necessitate a VAD often differs from adult heart failure (Table 88-1). For children, the most common etiologies of myocardial failure include postoperative failure to wean from cardiopulmonary bypass, congenital heart disease, cardiomyopathies, and acute myocarditis.[8,9] Children do not usually suffer from the typical adult problems of hypertension and ischemic heart disease. Congenital heart disease, for example, may entail elements of right and left ventricular (LV) and pulmonary dysfunction and cardiomyopathy with LV failure may result in elevated pulmonary vascular resistance (PVR). While biventricular support is available for such patients, the outcomes for patients with BiVAD (right and left) support are worse than those with univentricular support.[2] Furthermore, with the advent of pulmonary vasodilators, such as milrinone and sildenafil, patients with elevated PVR due to left heart failure may have near normalization of their pulmonary pressures following unloading of the diseased LV through the use of an isolated LVAD.

By assuming much of the responsibility for cardiac output, VADs may allow for the failing myocardium to recover or at least for the patient to have increased mobility and rehabilitation and improved nutrition if transplantation is required. Decompression of the cardiac chambers through mechanical assistance can lower wall stress, reduce myocardial oxygen consumption, and allow for recovery of the myocardium. Other advantages of VAD support include potentially lower requirements for inotropic and vasoactive agents that have, as some of their side effects, arrhythmias, peripheral vasoconstriction, and hyper- or hypotension. For those patients with reasonable pulmonary function, VADs offer isolated ventricular support without the need for oxygenation. In these patients (as opposed to patients on ECMO, for example), the benefits of not requiring an oxygenator in the circuit include potentially lower anticoagulation requirements, less platelet destruction, fewer bleeding complications, and the possibility of mobilization.

## CLINICAL FEATURES

Congestive heart failure in children is primarily attributable to congenital heart defects, cardiomyopathies, and myocardial dysfunction following cardiac surgical repair. The yearly incidence of heart failure from structural defects is 0.1 to 0.2 percent of live births, while the yearly incidence of cardiomyopathy in infants and children has been estimated to

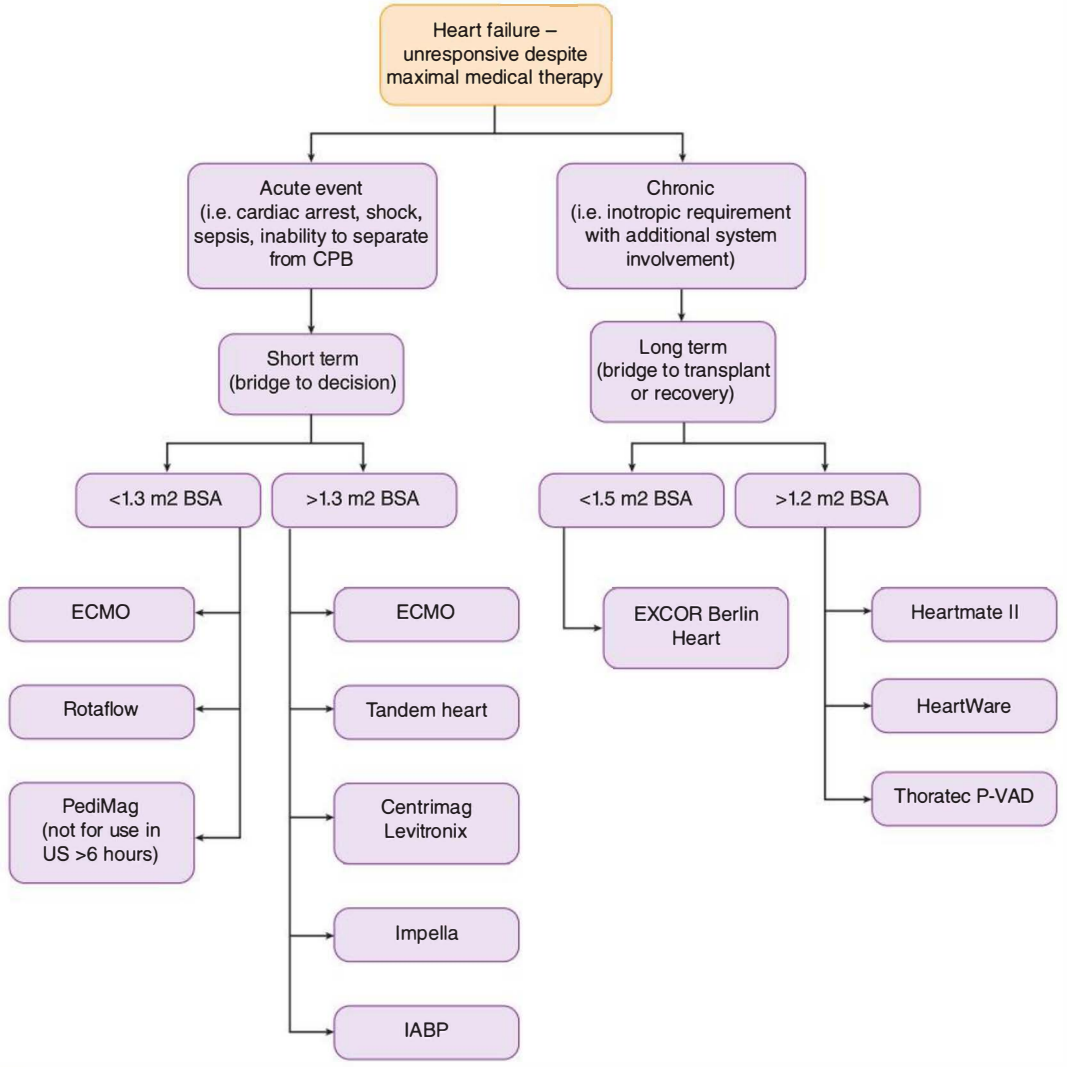



**FIGURE 88-1** Decision-making flowchart (in PowerPoint).

**TABLE 88-1: Common Causes of Pediatric Cardiac Failure**

| |
|---|
| Postcardiotomy |
| Congenital heart disease (with or without surgical intervention) |
| Acute myocarditis |
| Cardiomyopathy (dilated most common indication for VAD) |
| Toxins (chemotherapy) |
| Genetic dystrophy |
| Infection (viral) |
| Nutritional |
| Ischemic (Kawasaki disease) |
| Idiopathic |
| Hypertrophic |
| Cardiac arrest (postarrest ventricular dysfunction) |

be 0.6 in 100,000. The number of children being hospitalized with heart failure is increasing. In an analysis of 15 million pediatric hospitalizations in the US, it was reported that the number of children requiring hospitalization for heart failure increased by 25 percent between 2003 and 2006. During that time period, there was a 32 percent increase in patients hospitalized for heart failure whose underlying diagnosis was congenital heart disease, and a 14 percent increase in patients with cardiomyopathy. Furthermore, about 10 to 20 percent of those who have undergone complex repairs of congenital cardiac defects will develop heart failure by young adulthood.[2]

Aside from failure to wean from cardiopulmonary bypass, typical symptoms of heart failure in infants include tachypnea, tachycardia, failure to thrive, and poor feeding. Patients

may develop signs of congestion, including an enlarged cardiac silhouette on chest radiographs, pulmonary edema, and hepatic enlargement. In toddlers and older children, jugular venous distention and edema might be findings observed in association with growth failure and fatigue. As children become adolescents, the severity of heart failure can be classified as it is in adults, typically with the New York Heart Association (NYHA) functional classification.

If untreated, heart failure ultimately compromises end-organ perfusion, thus leading to the downward spiral of multi-organ system failure. Altered mentation, decreased urine output, rising creatinine, increasing liver function indices, and elevated lactic acid levels all point to inadequate perfusion. If cardiac output or perfusion pressures do not meet the metabolic demands of the body, persistent decline and circulatory collapse will ensue.

## INDICATIONS FOR VENTRICULAR ASSIST DEVICE IMPLANTATION

Initial therapy for pediatric heart failure will usually include diuretics (including aldosterone), and β-blockers as well as angiotensin-converting enzyme inhibitors and/or digitalis. As heart failure progresses, patients will require admission to the intensive care unit, along with inotropic and vasodilator support to maintain adequate cardiac output. Milrinone is most commonly used in these circumstances with the addition of low dose dopamine and/or low dose epinephrine if further inotropic support is necessary, realizing that all of these medications have the potential to result in development or worsening of arrhythmias. With worsening failure, patients may require intubation and ventilatory support, hemodynamic monitoring with a central venous or Swan-Ganz catheterization, close monitoring of renal function and placement of an indwelling urinary catheter. Adequate enteral nutrition must also be provided, usually by means of a feeding tube whenever possible.

The indications for VAD placement are much the same in larger children as in adults, even though the disease process is often different (Table 88-2). For smaller children, such as infants and toddlers, indications for VAD support are much more vague and often rely on clinical judgment. Signs such as recurrent ventricular arrhythmias, inability to feed and recurrent pulmonary edema are particularly ominous in this patient population. Some centers utilize involvement of more than one system as a potential trigger for VAD placement (Table 88-2). The inability to tolerate enteral feeds, for example, suggests worsening heart failure with decreased splanchnic perfusion. In pediatric patients, catastrophic collapse can occur with great rapidity and without the usual clinical warning signs often seen in adults. Near-death and resuscitation events, even when patients are stabilized, should not be given another chance to occur. In a medically optimized patient, elevated cardiac filling pressures along with persistent acidosis and hypotension indicate poor perfusion, often secondary to poor ventricular function. These

**TABLE 88-2: Indications for a Ventricular Assist Device**

1. Inability to wean from cardiopulmonary bypass - usually a short-term device
2. Persistent heart failure after maximal treatment with inotropic support with evidence of end-organ dysfunction in at least one other system:
   a. Neurolocical: altered mental status
   b. Cardiovascular: additional need for second inotrope or persistently low-mixed venous saturations (widening AV O2 gradient)
   c. Respiratory: need for intubation with mechanical ventilation or persistent need for noninvasive ventilation
   d. Renal: rising creatinine, fluid overload despite diuretic use
   e. Gastrointestinal: inability to tolerate enteral feeds, rising LFTs (liver function tests)
   f. Musculoskeletal: inability to ambulate or fatigue limiting activities

are the types of "gray-zone signs" that should lead one to contemplate institution of VAD support. In essence, if clinical deterioration secondary to heart failure continues despite maximal inotropic support, strong consideration should be given to insertion of a VAD.

Pediatric VADs are by definition "bridging" devices to either recovery or transplantation.[2,10] The concept of "destination therapy," which is gaining acceptance for the adult population, is not accepted for pediatric patients at this time. Ethical considerations (including futility and hopelessness) must also be addressed before placing a VAD, particularly in cases of cardiac arrest.

The indications for VAD placement can be divided into acute and chronic heart failure. This distinction may affect the choice of which device to place once the decision for VAD implantation has been made. For example, postcardiotomy patients can initially be maintained on VADs designed for short-term use. Options like ECMO may be equivalent if not better in this setting. Patients with chronic heart failure might benefit more from a continuous flow device (such as HeartMate II or HeartWare) or a pulsatile VAD (such as Berlin Heart EXCOR) that allow for earlier mobility and less lifestyle restrictions. There is a rising population of patients who will fail to wean successfully from "acute" devices and will need conversion to more "chronic" support.[11] This will increasingly become the case, as more pediatric VADs become available.

As pediatric VADs become more commonplace in clinical practice, new indications may arise for their utilization. Rather than merely representing a salvage procedure, VADs may become a standard adjunct for some complex congenital heart operations. One group of investigators has suggested routine ventricular assist after complex congenital reconstructions like the Norwood procedure, citing greater ease of postoperative management as an advantage.[12] With greater use and long-term follow-up, the indications for VAD placement will change and might be further broadened.

## SURGICAL THERAPY

At present, only a limited number of pediatric VADs are available in the United States. This should change in the near future, as promising results from European studies are being reported along with ongoing US studies as well. The range of mechanical assist devices for the pediatric heart includes ECMO circuits as well as pulsatile and nonpulsatile VADs. Intra-aortic balloon pumps (IABPs) are used much less frequently in the pediatric population. Although ECMO for cardiac support has been directly compared to nonpulsatile and pulsatile VADs in some series,[13] there are few data directly comparing one VAD to another.

### Intra-Aortic Balloon Counterpulsation

Although use of the IABP has greatly facilitated the management of adult patients with heart failure, adaptation to the pediatric population has not been as fruitful. The IABP is a biocompatible balloon that is introduced into the descending thoracic aorta and intermittently inflated/deflated (triggered by the electrocardiogram or blood pressure tracing) to augment diastolic blood pressure. By deflating prior to the initiation of systole, the device decreases afterload and thus ventricular work, by creating a "vacuum." During diastole, inflation of the balloon improves coronary as well as splanchnic perfusion. Pediatric anatomy and physiology have posed many obstacles for the use of this technology. Difficulty with insertion remains a challenge even with smaller designs, while higher pediatric heart rates make timing a significant challenge, particularly in a 1:1 setting. Moreover, some feel that the pediatric aorta is considerably more elastic and compliant than that of the adult, which limits the counterpulsation effect; this assertion has nevertheless been challenged.[14] Furthermore, most pediatric patients have unobstructed coronaries, rendering the increased coronary perfusion afforded by the IABP less relevant than it is in adults. Patients with IABP suffer from problems with thrombosis and emboli, as well as the destruction and consumption of cellular blood components, therefore requiring transfusion. For these reasons, the IABP has a limited role in the pediatric population.[15] Although they may be reasonable for short-term support in larger children, IABPs have a very limited role in their long-term mechanical support or bridging to transplantation.

### Extracorporeal Membrane Oxygenation

ECMO consists of a centrifugal or roller pump combined with an oxygenator, which is used for venoarterial or venovenous bypass (Fig. 88-2). Introduced in 1957, this modality has proven to be most useful for neonates with respiratory failure.

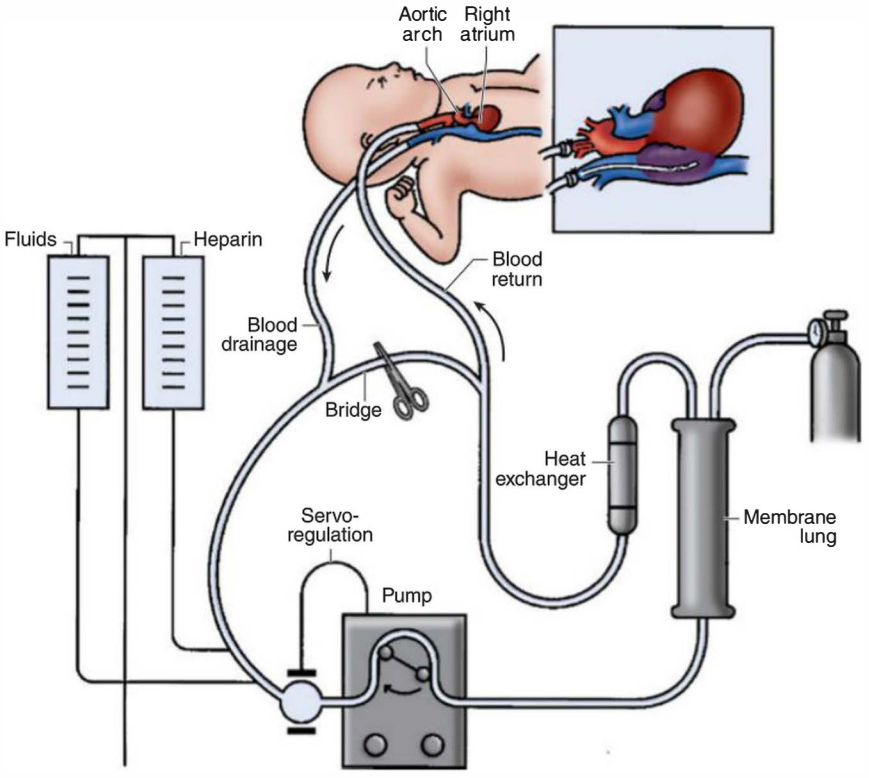



**FIGURE 88-2** Typical extracorporeal membrane oxygenation (ECMO) circuit with right common carotid/internal jugular cannulation.

However, it has also been utilized with success in pediatric cardiac failure. At this time, it is the most widely used method of pediatric ventricular support in the United States, mostly secondary to its availability and ease of placement. Unlike some other VADs, ECMO can be used for children of all sizes, from premature neonates to near-adults. It can be placed centrally (through the chest) or peripherally with either carotid artery and jugular vein or femoral artery and vein cannulation. Physiologically, venoaterial ECMO does result in a decrease in LV preload as well as an increase in LV afterload as ECMO flow is increased. Furthermore, without venting the left heart, it can result in increased ventricular wall stress because of the inability to decompress the left-sided cardiac chambers. Left atrial and ventricular distention occurs to a degree proportional to the number of aortopulmonary collaterals; it may be managed by venting the left atrium either directly or trans-septally via the right atrium.[16,17] ECMO by design improves arterial oxygenation and, if cannulated in a venoarterial fashion, acts to decompress and support both ventricles. For those patients with mainly pulmonary dysfunction (meconium aspiration, for example), ECMO can be instituted in a venovenous configuration, thereby improving venous blood oxygenation and myocardial oxygen delivery. Pulmonary hypertension resulting from low venous blood saturations may also be improved, allowing for some offloading of the right heart. Since the ECMO circuit involves both a pump and an oxygenator, it is reasonable that the pump alone may suffice for those patients without pulmonary insufficiency. By eliminating the oxygenator, it is possible to decrease the amount of foreign surface contact in the circuit, thus decreasing the inflammatory response. Moreover, if the venous cannula is placed in the left atrium or ventricle, the same pump may be used as a left VAD. For this reason, the most commonly used true VAD in the United States has been the centrifugal pump. ECMO is discussed in further detail in Chapter 87. For the purpose of this chapter, we categorize VADs into nonpulsatile and pulsatile types.

## Nonpulsatile Ventricular Assist Devices

### CENTRIFUGAL PUMP

The centrifugal pump has been the most widely used VAD in pediatric cardiac surgery. These VADs consist of inflow and outflow cannulas connected by a centrifugal pump for blood propulsion. Often, the same cannulas utilized during cardiopulmonary bypass may be used for the institution of postoperative ventricular support. Additional cannulation of a pulmonary vein, left atrial appendage, or the pulmonary artery will allow for univentricular or biventricular support. Centrifugal pumps do not generate pulsatile flow and are considered to cause less hemolysis than roller heads. Roller pumps are less portable and also pose a risk of raceway rupture with resultant gas embolism.[16,17]

Successful results using centrifugal VADs have been reported in children of all sizes, including one series of 35 neonates weighing less than 6 kg with postcardiotomy failure.[17] Sixty-three percent of these patients were successfully weaned from centrifugal pumps in this series. Patients may be weaned from these VADs by progressively decreasing the flow rate while observing the ventricular and hemodynamic response under echocardiographic guidance. Cardiac chamber dilation indicates inability of the native heart to maintain adequate cardiac output, thus necessitating continued support. If the patient fails to wean from the centrifugal pump within a few days, a decision to convert to a longer term bridging device or withdrawal of care should be considered. In a series from Boston studying pediatric patients who required VAD or ECMO placement, patients who were unable to wean from the VAD or ECMO within 72 hours either died or required cardiac transplantation. Lack of ejection (identified by pulsatility of the arterial line waveform) is also regarded as an adverse prognostic indicator for ventricular recovery.[18]

Centrifugal pump VADs are not designed for mobile patients; most remain intubated, sedated, and sometimes pharmacologically paralyzed while recovering. In summary, the centrifugal pump is essentially an ECMO circuit deprived of an oxygenator. The advantage to this type of VAD is avoidance of blood trauma known to be caused by the oxygenator; as well as the ability to minimize anticoagulation in the persistently bleeding patient; however, if a patient has pulmonary compromise or intracardiac shunts, ECMO is probably the better choice for short-term supportive care. Also, most neonates requiring postcardiotomy ECMO will have combined respiratory and cardiac failure.

### AXIAL FLOW PUMPS

Axial flow pumps (Hemopump, MicroMed DeBakey VAD-Child, Jarvik 2000, HeartMate II, Heartware, Streamliner, Impella system, Valvo pump, the IVAP VAD, and Berlin

**TABLE 88-3: FDA-Approved Pediatric VADs**

| Device | Size or Age Limits | Ventricular Support | Use Classification | Anticoagulation Regimen |
|---|---|---|---|---|
| Berlin Heart EXCOR | <1.5 $m^2$ (available for larger patients but not FDA-approved >1.5 $m^2$ BSA) | Left, right or biventricular | Pulsatile, paracorporeal | Heparin initially<br>Then warfarin or enoxaparin<br>With aspirin + dipyridamole |
| HeartAssist 5 (formerly DeBakey VAD Child)® | 5–16 years old with BSA >0.7 $m^2$ and <1.5 $m^2$ | Left | Continuous axial flow; intracorporeal<br>HUD use | Heparin initially<br>Then warfarin<br>With aspirin ± clopidogrel |

**TABLE 88-4: FDA-Approved Adult VADs with Potential Application in Larger Children**

| Device | Size or Age Limits | Ventricular Support | Use Classification | Anticoagulation Regimen |
|---|---|---|---|---|
| HeartMate II | >1.2 $m^2$ BSA (<1 possible) | Left | Continuous axial flow; intracorporeal | Infrequent post-op use of heparin<br>Warfarin (INR 1.5–2.5)<br>Aspirin 81 mg (same for HM XVE) |
| HeartWare (HVAD) | >1.2 $m^2$ BSA | Left | Continuous centrifugal flow; intracorporeal | Warfarin (INR 2–2.5)<br>Aspirin 325 mg |
| Thoratec PVAD | >0.73 $m^2$ BSA (smallest to date) | Left, right or biventricular | Pulsatile, paracorporeal | Heparin initially<br>Then warfarin or enoxaparin ± aspirin or other antiplatelet therapy |
| Thoratec IVAD | >0.89 $m^2$ BSA (smallest to date) | Left, right or biventricular | Pulsatile, intracorporeal | Heparin initially<br>Then warfarin or enoxaparin ± aspirin or other antiplatelet therapy |
| Jarvik 2000 | >1.5 to <2.3 $m^2$ BSA | Left | Continuous axial flow; intracorporeal | Heparin initially<br>Then warfarin<br>With aspirin ± other antiplatelet therapy |
| Abiocor TAH | >1.7 $m^2$ BSA | Biventricular | Intracorporeal | Heparin initially<br>Then warfarin<br>With aspirin ± other antiplatelet therapy |
| SyncardiaCardioWest TAH | >1.7 $m^2$ BSA | Biventricular | Pulsatile, intracorporeal | Heparin initially<br>Then warfarin<br>With aspirin ± other antiplatelet therapy |
| Novacar | >1.5 $m^2$ BSA | Left | Continuous axial flow; intracorporeal | Heparin initially<br>Then warfarin<br>With aspirin + other antiplatelet therapy |

INCOR) are some of the devices in an emerging technology that aims at incorporating nonpulsatile flow into miniaturized devices that support pediatric heart failure patients; this is the focus of the PumpKIN trial previously mentioned. Tables 88-3, 88-4, 88-5, and 88-6 list some of the more common devices currently available with a description of the devices under the NIH trial.[19] They are typically small, tubular, implantable rotary pumps connected either directly to the ventricle or to inflow and outflow cannulas. They operate at higher rotational speeds than centrifugal pumps and generate higher flow with lower increases in pressure. They operate at slightly less power, which might, in turn, facilitate the development of lighter and more portable power supplies in the future. There is a growing experience with axial flow pumps in larger pediatric patients, which has been reported. Considering their smaller size and the possibility of implantation via a left thoracotomy, these pumps may become a viable option for VAD support in children awaiting transplant.

## Pulsatile Ventricular Assist Devices

The Berlin Heart EXCOR is a device specifically designed for children. There have also been reports of adult pulsatile

**TABLE 88-5: Temporary Mechanical Assist Devices**

| Device | Max Cardiac Output/Flow Rate; Type of Pump | Approximate Maximum Duration | Anticoagulation |
|---|---|---|---|
| ECMO | Depends on cannula size; centrifugal | Approx 30 days | Heparin |
| Tandem Heart | 5–8 L/min; centrifugal | 14 days | Heparin (through infusing system of pump) |
| AbiomedImpella 2.5 | 2.5 L/min; microaxial | 6 h–7 days | Heparin for placement and weaning/removal |
| Rotaflow | 10 L/min; centrifugal | Several weeks | Heparin |
| Levitronix | 10 L/min; centrifugal | 14 days | Heparin<br>Antiplatelet therapy |
| Pedimag | 2.5 L/min; centrifugal | 6 h–7 days (approved in US for 6 h use only) | Heparin |

**TABLE 88-6: NIH PumpKIN Trial (Pumps for Kids, Infants and Neonates)—Clinical Trial to Begin in 2013**

| Program | Device |
|---|---|
| University of Pittsburgh | PediaFlow |
| Ension, Inc | Pediatric Cardiopulmonary Assist System |
| Jarvik Heart, Inc | Pediatric Jarvik 2000 |
| University of Maryland/ Levitronix, LLC | PediPL |

VADs (Thoratec, Novacor, Abiomed) adapted in larger children with some success. Although there are various different designs, most of these devices involve inflow and outflow cannulas, a pneumatically driven pump with air and blood chambers separated by a biocompatible membrane, and valves that assure unidirectional flow. They are mostly paracorporeal units and require central cannulation of the heart and great vessels.[20,21]

Patients with pulsatile VADs have been shown to have fewer bleeding complications,[22,23] fewer severe infectious complications and, of course, increased mobility when compared to children treated with ECMO; importantly, they can often be weaned from mechanical ventilation, become more mobile and have improved nutrition. To date, pulsatile VADs have been more effective in treating myocarditis and cardiomyopathy patients than postcardiotomy patients.

The Thoratec pVAD is a pneumatically driven paracorporeal pump with mechanical valves and a maximum stroke volume of 65 mL (Fig. 88-3). In a recent review, a total of 101 children (under 18 years of age) received a Thoratec VAD. Anticoagulation was achieved initially in the postoperative period with heparin, with a goal aPTT of 60 to 80 seconds. The anticoagulation regimen was changed to warfarin once the patient was tolerating an enteral diet, with a target international normalized ratio (INR) of 2.5 to 3.5, which is similar to protocols designed for adults. Overall, 66 patients survived to transplant while 10 were bridged to recovery and VAD explantation. Preoperative weight was greater than 20 kg in all but one patient, with the majority of children weighing more than 50 kg. Pediatric patients supported by Thoratec fared better if treated for myocarditis or cardiomyopathy than for postcardiotomy rescue or congenital heart disease. Patients who had LV cannulation had fewer neurologic events than those who were cannulated via the left atrium.[24]

The Abiomed BVS 5000 is a pneumatically driven pump with an electromagnetic console, a gravity-filled chamber, and an air-actuated ventricular chamber to induce pulsatile contractions (Fig. 88-4). It is intended for use as a short-term device. It has been used successfully though only sporadically in a few pediatric patients, all of whom were adolescents.[10] No series have been reported with this device in smaller children.

The Berlin Heart EXCOR assist device is the European counterpart of the Thoratec VAD; however, it has been successfully modified to fit smaller patients (Fig. 88-5). The Berlin Heart is also a pneumatically driven paracorporeal pump with either tilting-disk or trileaflet polyurethane valves. The pump is available in numerous stroke-volume sizes down to 10 mL, and there are different size cannulas. By 2011, over 900 patients have been supported by a Berlin Heart EXCOR device. Anticoagulation is initially maintained with heparin infusion to maintain aPTT between 60 and 80 seconds with an anti-Xa level of 0.3 to 0.7 IU/mL. In the recently published review (2012), thromboelastography has also been incorporated into coagulation evaluation and management. Ultimately, patients require aspirin, dipyridamole and either warfarin or enoxaparin for long-term anticoagulation. Overall, 88 percent of the participants with body surface area <0.7 $m^2$ (cohort 1) and 92 percent of those with BSA between 0.7 to 1.5 $m^2$ (cohort 2) survived to undergo either heart transplantation or weaning from the device. The most common serious adverse events in this study were major bleeding (in 42 percent of participants in cohort 1 and in 50 percent of those in cohort 2),



**FIGURE 88-3** Thoratec VAD.



**FIGURE 88-4** Abiomed BVS 5000.



FIGURE 88-5 Two month-old, 4.5 Kg infant with Berlin Heart LVAD Excor implanted at the Johns Hopkins University Hospital.

infection (in 63 and 50 percent, respectively), stroke (in 29 and 29 percent), and hypertension (in 50 and 33 percent).[2,10,25]

The Medos assist device is another European pneumatically driven paracorporeal pump designed to accommodate pediatric patients, with pump stroke volumes as low as 10 mL, as well as several different size cannulas (Fig. 88-6). The device is, however, not approved by the FDA if not for compassionate use. Anticoagulation is achieved with intravenous heparin and oral antiplatelet therapy with aspirin. Of 56 patients with known outcome supported by the Medos device, 11 survived to transplantation and 10 were weaned to recovery, for an overall survival rate of 37.5 percent.[20] Again, there was a trend toward a greater survival advantage in patients treated for cardiomyopathy than for postcardiotomy patients.

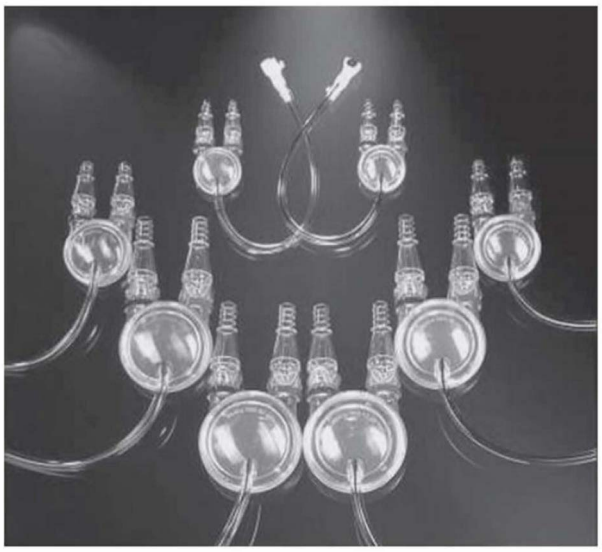


FIGURE 88-6 Medos VAD.

The Toyobo VAD is a Japanese model with 20-mL stroke volumes and a maximal output of 2.4 L/min; it was reportedly implanted in eight patients.[26] Three of the patients were weaned and none ultimately survived in this small series. Nevertheless, with further refinement and development, this VAD might have pediatric applications in the future.

## SURGICAL CONSIDERATIONS

### Peripheral Cannulation

The most common technique involves a cutdown of the right carotid artery and jugular vein. Alternatively, the femoral artery and vein may be used; the former approach is most commonly applied, while maintenance of perfusion to the lower extremity should be a concern when performing the latter. An appropriately sized cannula is placed in each vessel and securely fixed. Meticulous de-airing is performed during all connections. The carotid artery must be either ligated or reconstructed after successful weaning from peripheral support such as ECMO.

### Central Cannulation

Numerous techniques and sites have been used for both inflow and outflow cannulas (Table 88-7).

Initiation of LVAD support in a patient already on cardiopulmonary bypass is usually accomplished with standard bypass cannulas inserted through the superior pulmonary vein into either the left atrium or across the mitral valve into the LV. Alternatively, the LV apex can be cannulated directly. This may minimize neurologic complications and improve pump inflow, leading to superior flow rates. This is also the

**TABLE 88-7: Inflow and Outflow Cannulation Options**

| Device | Inflow | Outflow |
|---|---|---|
| LVAD | LV apex (most common)<br>Left atrium | Ascending aorta |
| RVAD | Right atrium | Pulmonary artery |
| BIVAD | LVAD inflow<br>RVAD inflow | LVAD outflow<br>RVAD outflow |
| VA ECMO | • Internal jugular vein (neck cannulation)<br>• Right atria (chest cannulation)<br>• Femoral vein (groin cannulation) | • Internal carotid (positioned just above aortic arch)<br>• Ascending aorta (chest cannulation)<br>• Femoral artery (groin cannulation) |

access utilized for most long-term LVADs. If only an RVAD is to be utilized, inflow is via the right atrium and return into the pulmonary artery.

If postcardiotomy ECMO is required, venous cannulation is via the right atrium and return directly into the aorta, utilizing the cannulas that have been utilized during the procedure.

## CLINICAL ISSUES

### Anticoagulation

Anticoagulation is used for all pediatric VADs, although the regimen varies by device. One of the major technical difficulties with developing pediatric VADs involves the thrombogenicity of smaller devices.[27,28] Although there may be slight variations in company recommendations, full anticoagulation is recommended for all pulsatile devices to keep the aPTT between 60 and 90 seconds with an anti-Xa level of 0.3 to 0.7 IU/ml. The use of thromboelastrography is also incorporated into the Berlin Heart EXCOR anticoagulation protocols. If the patient is converted to an oral anticoagulation strategy (warfarin), an INR of 2.5 to 3.5 is usually recommended. Some centers may use enoxaparin instead of warfarin. This regimen does contribute significantly; however, to the bleeding episodes associated with VADs. The risk of thrombosis with resultant embolic phenomena must therefore be weighed against the severity of bleeding as measured by transfusion requirements and hemodynamic instability. Antiplatelet therapy is also utilized in many VAD protocols, with the use of aspirin and potentially other antiplatelet agents. Light aggregometry may be used to evaluate the desired block in particular platelet pathways.

For continuous flow devices, such as the HeartMate II, postoperative heparin is not routinely used due to the incidence of bleeding in the initial clinical trial patients. Instead, patients are started on warfarin and aspirin therapy within a few days postimplant. Of note, most patients will develop acquired von Willebrand deficiency and will need to be monitored for bleeding. In the postapproval study, the rate of ischemic stroke was 4.7 percent, with hemorrhagic stroke rate of 1.2 percent.

Regardless of device used, the highest risk for thrombus formation during VAD therapy occurs with infection or inflammation, resulting in increased WBC counts and prothrombotic tendencies. It is imperative to reevaluate the anticoagulation levels for these patients during these periods of higher risk, as increases in anticoagulation therapy may be needed.[29]

As mentioned above, antithrombotic medications are often utilized as well in an effort to reduce anticoagulation requirements and improve safety margin. For example, Berlin Heart EXCOR technology utilizes heparin coating within the VAD chambers to protect against thrombogenesis. Further development of circuit coating might reduce anticoagulation requirements and therefore bleeding complications that often accompany the use of VADs.

### Antibiotic Prophylaxis

Routine antibiotic prophylaxis is mandatory in the perioperative phase. Prophylaxis against gram-positive microorganisms is usually all that is indicated in an otherwise uninfected patient. First-generation cephalosporins are our first choice; these should be given 30 min prior to skin incision for VAD placement and are routinely administered for 24 hours postoperatively. Any signs of infection must be addressed aggressively.

### Infection

Despite the use of strict aseptic techniques during both the insertion and maintenance of VADs, infections continue to be a major cause of morbidity and mortality.[30] Any suspicion of infection should be aggressively managed with immediate cultures and the administration of broad-spectrum antibiotics, followed by change to a more targeted regimen as soon as culture results and sensitivities are available. Very little has been published regarding pediatric VAD infections; some have advocated antifungal prophylaxis in adults at least for the early perioperative period.[24] Adult studies have shown device-related infections to be very serious and often fatal. Treatment must include timely antimicrobial therapy, surgical drainage or debridement, and, sometimes, device removal. As noted above, reevaluation of anticoagulation levels is necessary as well to ensure appropriate anticoagulation.

### Bleeding

Owing to the need for anticoagulation, bleeding is an inherent risk that can lead to devastating complications. Intracerebral hemorrhage occurs in 5 to 15 percent of patients supported with pulsatile VADs,[21] with the majority of these proving to be fatal. In the NEJM study previously mentioned, 42 to 50 percent of study patients developed major bleeding. However, other studies that specifically compared the blood transfusion requirements of patients on ECMO versus those supported with a Berlin Heart have found that patients with the Berlin Heart required significantly less blood, platelet, and plasma replacement than those on ECMO.[23]

### Neurologic Complications

Poor neurologic outcomes following institution of cardiac support are often multifactorial in etiology, including underlying disease, duration and severity of low-cardiac-output state as well as complications of bleeding and thromboembolism due to the assist device. In reviewing long-term follow up of children with cardiac disease who required mechanical support, poor neurologic outcomes were more common in ECMO survivors (60 percent) than nonpulsatile VAD survivors (20 percent). Finally, LV cannulation might lower the

risk of neurologic events in patients with pulsatile VADs.[16] In the Berlin Heart EXCOR study by Fraser et al. published in 2012, 29 percent of children were found to have neurologic complications.[2]

## Multidisciplinary Ventricular Assist Device Management

Due to the complexities of management, choice of device, timing of implant, potential for infectious disease evaluation and the complex interplay between inflammation and thrombosis, it is important to develop a multidisciplinary group to systematically evaluate patients with end-stage heart failure that requires VAD support particularly in light of the often infrequent use in many pediatric hospitals.

# CONCLUSIONS

In comparison to the adult population, development of pediatric VADs is still in its relative infancy. However, as technology continues to improve, VADs are likely to become invaluable tools in the treatment and management of both acute and chronic heart failure in children. The decision of which device to use must be tailored to the individual patient. While for many years it has been thought that it was necessary to maintain physiologic pulsatility for long-term support, reports describing the use of HeartMate II and HeartWare devices in adolescents and young adults have shown that the use of continuous-flow devices does not result in end-organ damage, and that the rates of thrombosis and hemorrhage are significantly lower. Ongoing pediatric trials may in fact reveal that miniaturized continuous-flow devices are effective, with lower complication rates. Clinicians must also continue to investigate different anticoagulation regimens in order to maximize prevention of thrombosis and bleeding.

As pediatric patients survive the initial insult of acute cardiac failure with the assistance of short-term VAD support, they must be weaned, changed to more suitable long-term VAD support, or transplanted. Decisions must often be made quickly, before refractory infections or end-organ failure occur. As transplantation is limited by organ availability, there is currently a real need for reliable, long-term VADs in small children. As further research and development advances in the field of cardiac support, pediatric patients will hopefully have in the future more treatment options to improve long-term survival.

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## VENTRICULAR ASSIST DEVICES IN CHILDREN BOARD REVIEW QUESTIONS (CHAPTER 88)

1. A 3-year-old patient develops desaturations to 82 percent in the PICU after placement of a Berlin Heart LVAD. CXR shows good position of the ETT and no mediastinal widening. On 50 percent $FIO_2$, the ABG is 7.29/57/74/23. The SBP 78/40 on a moderate dose milrinone infusion. Which of the following is *not* appropriate therapy?
   A. Temporarliy increase $FIO_2$ to 100 percent
   B. Initiate nitric oxide therapy
   C. Increase ventilatory rate
   D. Increase LVAD rate
   E. Obtain an echocardiogram

2. A 14-year-old patient is post-op day #2 after Heartmate II LVAD, now post-op day #2. She remains intubated with some end-organ dysfunction, including renal and liver dysfunction. The patient is on a heparin infusion for left common femoral vein thrombus, and the platelet count has declined from 125,000 to 42,000. Which alternative anticoagulation therapy is most appropriate?
   A. Bivalirudin
   B. Lepirudin
   C. Argatroban
   D. Warfarin
   E. Enoxaparin

3. A 9-month-old patient with dilated cardiomyopathy is admitted for worsening heart failure. ECHO reveals EF 10 percent with no effusion and severe biventricular failure. Of the following, which support device is most suitable for this patient as a bridge to transplant?
   A. Heartmate II
   B. Heartware
   C. IABP
   D. Berlin Heart
   E. Total artificial heart

4. You have just inserted a Berlin Heart LVAD in a 4-year-old patient with dilated cardiomyopathy. Upon weaning from bypass, the patient's saturations decrease to 79 percent, systemic BP decreases to 60/30, and CVP increases to 22. Which of the following could explain these events?
   A. Inadequate LV decompression
   B. Outflow graft obstruction
   C. Tamponade
   D. Right heart dysfunction
   E. All of the above

5. Of the following, the clinical condition *least* likely to be managed successfully with an LVAD is:
   A. Dilated cardiomyopathy
   B. Postcardiotomy failure
   C. Cardiogenic shock from myocarditis
   D. Failing Fontan
   E. Cardiac arrest after Norwood reconstruction

## ANSWERS

1. **Answer: D.** This patient is experiencing a pulmonary hypertensive crisis, such that the LVAD is not filling due to lack of forward flow from the right heart. Simply increasing the LVAD rate will have little effect on the clinical situation. Pharmacologic relaxation of the reactive pulmonary vasculature includes increasing oxygen concentration until other therapies take effect, as well as NO, milrinone and correcting the $PCO_2$ with improved ventilation. Volume resuscitation and BP stabilization may also be necessary in the initial phase. Tamponade is another important consideration that can result in poor LVAD filling which can be rapidly diagnosed with echocardiography.
2. **Answer: A.** The concern is for heparin-induced thrombocytopenia (HIT), and anticoagulation using a non-heparin agent is appropriate. Bivalirudin is metabolized by a combination of renal mechanisms and proteolytic cleavage, but is less toxic to the kidneys than lepirudin (which is primarily metabolized through the kidney). Argatroban is cleared primarily through hepatic metabolism. Warfarin is not appropriate this soon after surgery and has delayed onset. Enoxaparin is low-molecular weight heparin that can also result in HIT.
3. **Answer: D.** Mechanical support may be necessary if end-organ function is beginning to be compromised, particularly in this age patient. Given the patient's age and size, the Berlin Heart would be most appropriate. Patients under 1 year of age may wait 6 months or longer on the heart transplant waiting list, depending on a variety of factors, such as blood type. There are no continuous flow VAD devices currently FDA approved for infants in the US, but there is a large ongoing NIH trial investigating such devices in the smaller pediatric population.
4. **Answer: E.** Pulmonary edema from LV distension and high left atrial pressure can occur if LV decompression is not achieved, or with outflow graft obstruction. Right heart dysfunction and tamponade will independently decrease filling of LVAD. All of these conditions can lead to elevated CVP with hypotension.
5. **Answer: D.** Fontan physiology is the least likely to be successfully managed with an isolated LVAD, as it is very difficult to maintain adequate pulmonary blood flow. All of the other conditions are indications for ventricular assistance.

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# Pediatric Cardiac Transplantation

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**KEY CONCEPTS**

- Epidemiology
  - Since 1982, over 8000 pediatric heart transplants have been recorded in the Registry of the International Society of Heart and Lung Transplantation. The current number of reported pediatric heart transplants is about 450 per year, which originate in 80 global centers.
- Indications
  - Heart transplantation is the most effective and often the only treatment for end-stage pediatric heart disease. Complex congenital heart disease is the main indication for heart transplantation in infants, whereas end-stage cardiomyopathy is the main indication after the first year of life.
- Contraindications
  - The main contraindication is elevated pulmonary vascular resistance that is unresponsive to oxygen and vasodilators.
- Techniques
  - Heart transplantation is performed using either biatrial or bicaval techniques, depending on the size of the recipient child. Graft procurement and implantation are modified to accommodate the specific anatomic variations present in recipients with congenital heart disease.
- Outcomes
  - Mortality while waiting for a donor is 12 to 40 percent. The overall actuarial survival at 10 years is 66 percent. It is 74 percent for newborn recipients. Causes of mortality include graft rejection and failure, infection, cardiac allograft vasculopathy (CAV) (16 percent), and malignancy (8 percent).

## BACKGROUND

The quest for clinical cardiac transplantation (CT) originated in research laboratories of the 1960s. Principal North American investigators included Norman Shumway and Richard Lower at Stanford University in California and Adrian Kantrowitz at Albert Einstein College of Medicine in New York, among others. While Shumway and Lower were focused on the potential for CT among adults, Kantrowitz' studies were aimed at young infant recipients. At Stanford, investigators were learning the difficult balance between control of the host immune response and lethal opportunistic infections. Utilizing immunosuppressants of that era, adult laboratory animals were beginning to achieve survival of more than a year following orthotopic CT. In New York City, Kantrowitz observed that transplanted puppies experienced prolonged survival, even without immunosuppression. Then, unexpectedly, came news from Capetown, South Africa, that Christiaan Barnard and his team had accomplished the first clinical human CT.[1] On December 3, 1967, 55-year-old Louis Washkansky underwent orthotopic CT. He died of pneumonia 18 days later, but the celebrated transplant stimulated global interest, and a bevy of similar transplants. The vast majority of these early recipients experienced abbreviated survival, dying of rejection, infection, or both.

Just 3 days after the South African transplant, the first infant (neonatal) CT was attempted by Kantrowitz. The heart of an anencephalic infant was transplanted "off-pump" (i.e., with surface-induced hypothermia alone), into a neonate with severe Ebstein anomaly. The baby appeared to have a satisfactory operative procedure, but died suddenly and without clear explanation 6.5 h later. Kantrowitz did not pursue pediatric CT, and it would be 16 years before neonatal CT was to be attempted again. With the advent of cyclosporine for selective control of the cellular immune response,[2] clinical pediatric CT was successfully performed in the summer of 1984. Eric Rose, of Columbia University, transplanted a 4.5-year-old boy. Then, Douglas Behrendt performed CT in a 2-year-old girl at the University of Michigan. Neonatal CT was once again attempted on July 30, 1984 by Magdi Yacoub in London. The infant, who had hypoplastic left heart syndrome (HLHS), lived 18 days with an allograft from a Dutch infant donor.

On October 26, 1984, one of the authors (Leonard L. Bailey) performed CT on a premature human newborn with HLHS using the heart of a 9-month-old female baboon. The infant recipient became known as Baby Fae. She lived 3 weeks, dying of incompletely understood mechanisms. Her experience raised social and professional consciousness about the potential for infant CT. This new awareness led to the first successful neonatal CT, which occurred at Loma Linda University (LLU) on November 15, 1985.[3] The recipient was near death from HLHS at 4 days of age, when a distant neonatal donor was identified and transferred to LLU. The newborn recipient, now fully grown and gainfully employed, turned 27 years old in the fall of 2012. Additional infant allograft CTs were accomplished as procurement agencies began to take note of this donor organ resource. Throughout the decade of the 1990s, pediatric recipients produced major growth in the number of CTs performed worldwide.

Since 1982, CT has been recorded by the Registry of the International Society for Heart and Lung Transplantation (ISHLT) in over 8000 pediatric recipients. The incidence of pediatric CT has plateaued, with about 450 infant and childhood recipients reported annually to the ISHLT Registry. Today, infants and children (0–18 years old) constitute 12.5 percent of all reported recipients of CT.[4]

This chapter reviews indications for and contraindications to pediatric CT, timing for surgery, surgical techniques, immunosuppression regimens, rejection surveillance, complications, outcomes (highlighting the LLU experience), and future trends.

## INDICATIONS

CT provides the most effective treatment for end-stage heart disease, whether myopathic or congenital. Complex congenital heart disease remains the primary indication for CT among patients in the first year of life. Over the past decade, however, increasing numbers of CTs have been performed in infants for both primary and secondary cardiomyopathy, or for failure of single ventricle physiology. End-stage primary cardiomyopathy (including "burned-out" congenital heart disease) is the predominant indication for transplantation among recipients who are beyond the first year of life. Retransplantation accounts for 5 percent of all pediatric CT (Table 89-1).[4] The various cardiac diagnoses (myopathic and congenital) that may be considered for orthotopic pediatric CT are shown in Tables 89-2 and 89-3.

**TABLE 89-1: Indications for Pediatric Cardiac Transplantation Based on Age**

| Indication (%) | <1 year | 1–10 years | 11–17 years |
|---|---|---|---|
| Congenital | 63 | 36 | 24 |
| Myopathy | 31 | 55 | 64 |
| Other | 5 | 3 | 7 |
| Retransplant | 1 | 6 | 7 |

Adapted with permission from Hertz MI, Aurora P, Christie JD, et al. Scientific Registry of the International Society for Heart and Lung Transplantation: introduction to the 2009 Annual Reports. *J Heart Lung Transplant*. 2009;28(10):989–992.

## CONTRAINDICATIONS

The main contraindication to CT is elevated pulmonary vascular resistance (more than 5 Woods units) that is unresponsive to oxygen, intravenous vasodilators, and inhaled nitric oxide. Children with a transpulmonary gradient greater than 15 mm Hg are largely unsuitable for isolated CT.[5] Pulmonary vascular resistance is seldom an issue during early infancy, but it can become an important contraindication in older children and adolescents. Other contraindications are listed in Table 89-4. They include multisystem organ failure, active neoplasia, profound neurologic dysfunction, untreated clinical infection, and severe chromosomal abnormalities that limit survival, among others.

**TABLE 89-2: Cardiomyopathies that may be an Indication for Orthotopic Cardiac Transplantation**

Dilated—75%

Restrictive—12%

- Less amenable to medical or surgical therapy than other forms of cardiomyopathy
- High incidence of pulmonary hypertension and thromboembolic events

Hypertrophic—5%

- One-fourth of all hypertrophic cardiomyopathies include syndromes such as Noonan and Beckwith–Wiedemann

Myocarditis—8%

Distribution of cardiomyopathy subtypes within Pediatric Heart Transplant Study Group recipients transplanted.[29]

**TABLE 89-3: Congenital Cardiac Malformations that may be an Indication for Orthotopic Cardiac Transplantation**

Hypoplastic left heart syndrome (hypoplastic aortic tract complex)
Hypoplastic left heart equivalent:

- D-TGA with hypoplastic right ventricle and aortic tract
- Single ventricle with hypoplastic aortic tract
- L-TGA with single ventricle, heart block, and aortic tract hypoplasia
- Shone complex, including severe mitral valve stenosis, left ventricular outflow obstruction, coarctation of the aorta

Symptomatic severe Ebstein's anomaly with normal pulmonary arteries
Multiple obstructive rhabdomyomas or fibromas
Pulmonary atresia/intact ventricular septum (large coronary-dependent sinusoids)[a]
AV septal defect with hypoplastic left ventricle and mitral component (frequently associated with coarctation)
Single ventricle with subaortic obstruction (bulboventricular foramen)
Severe intrauterine AV valve insufficiency and ventricular dysfunction
Straddling AV valve and tensor apparatus
Complex truncus arteriosus
Severe congenital cardiomyopathy at end-stage with maximal medical management

AV, atrioventricular; D-TGA, D-loop transposition of the great arteries; L-TGA, L-loop transposition of the great arteries.

[a]Diminutive right heart malformations must have adequate-size right and left pulmonary arteries. Neonates unresponsive to $PGE_1$ may require placement of a systemic-pulmonary shunt while waiting for a donor.

## TIMING

Proceeding with CT is a team decision and is multifactorial. Pretransplant evaluation of potential recipients should be expeditious, leading to early registration with the national organ procurement and distribution center. Delay leads to unnecessary morbidity and mortality. Even when registered, a potential recipient's waiting time is entirely unpredictable. A waiting recipient may encounter major morbidities, such as overwhelming sepsis, cerebral hemorrhage, necrotizing enterocolitis, cardiac arrest, and hepatorenal failure, among others. Such morbidities may become contraindications to CT.

**TABLE 89-4: Clinical Conditions that may Contraindicate Orthotopic Cardiac Transplantation**

Marked prematurity (<34–36 weeks)[a]
Excessively low birth weight[a]
Active malignancy
Multisystem organ failure
Recalcitrant acidosis with pH <7.0
Abnormal neurologic status, suggesting a poor long-term prognosis[a]
Active, untreated infection
Genetic anomalies or syndromes that significantly limit survival
Socioeconomic factors leading to noncompliance[a]
Hypoplastic obstructive pulmonary veins
Hypoplastic left heart syndrome with intact atrial septum
Fixed pulmonary vascular resistance (>5 Woods units)

[a]Relative contraindications.

Recipients with complex congenital heart disease who are not candidates for surgical repair or palliation are listed early for primary CT. An occasional infant with unmanageable primary cardiac tumor or those with severe familial cardiomyopathy are also registered early for CT. Older pediatric recipients are typically listed for CT when they become resistant to medical management for congestive heart failure (CHF) and/or malignant arrhythmias, or when they fail to respond favorably to palliated single-ventricle physiology. Progressive deterioration, failure to thrive, and poor quality of life, even with optimal medical care indicate the need to list for CT. Also, patients with progressive pulmonary hypertension that might preclude transplantation at a later date are being listed more expeditiously.[6] As indications for CT have expanded, and as organ supply has remained constant, recipient waiting time and morbidity have increased. Mortality while waiting for a donor heart graft ranges between 12 and 40 percent.

Mechanical circulatory support as a bridge to pediatric CT has become increasingly important. Extracorporeal membrane oxygenation (ECMO, Chapter 87) is useful only for relatively short periods, but may bridge to a more durable device.[7] Utilization of infant-sized ventricular assist devices (VADs, Chapter 88) has proved to be a viable option for bridging to CT, similar to their use in older children and adolescents. VADs have been shown to improve waiting time survival without negatively affecting CT outcome.[8] Early listing for CT optimizes recipient survival and reduces the need for intermediate mechanical circulatory support.

## PROCUREMENT OF THE DONOR HEART GRAFT

Donor heart recovery is tailored to the individual anatomic demands of the recipient. En bloc excision of the heart, the central pulmonary arterial tree, the superior vena cava (SVC) in continuity with the brachiocephalic vein and the origin of the internal jugular veins, and some or all of the aortic arch may be required to simplify recipient reconstruction. Concomitant lung donation may not be suitable when replacement of the main and branch pulmonary arteries is anticipated in a recipient, or when a recipient has situs inversus or anomalous pulmonary venous connections. A general rule of thumb is to obtain more, rather than less, of what the recipient will require. Aggressive trimming of the donor heart is postponed until its implantation into the recipient.

Heart recovery is usually accomplished in concert with the recovery of other organs (by other teams) through a long midline incision. The donor is given 25 mg/kg of cephalosporin antibiotic and 10 to 25 mg/kg of methylprednisolone. Fifty percent dextrose (0.5–1.0 mL/kg) is administered

intravenously to the donor every 15 minutes until the organ is excised. The aorta is separated from the pulmonary artery, and the aortic arch vessels are doubly ligated and divided. The SVC and the innominate vein (as needed) are isolated. The azygous vein is ligated and divided. Its posterior location becomes a landmark for the future SVC anastomosis, or it can be used to enlarge the donor SVC if there is size discrepancy. Both pleural spaces are opened to accommodate drainage. When each team has completed their dissection, the donor receives intravenous heparin in a dose of 500 U/kg, and the heart is decompressed by transecting the inferior vena cava (IVC) and both of the left pulmonary veins. The aorta is cross-clamped, and 250 to 500 mL of antegrade cold crystalloid cardioplegia is administered by gravity infusion while the heart is being removed. The authors utilize cold Roe's solution for myocardial protection. An infusion volume of 50 to 75 mL/kg is used in neonates and smaller children. The idea is to gently chill the heart, but not freeze it. Cardiectomy is completed by lifting the heart upward; the posterior attachments, including the right pulmonary veins, are divided. The SVC, the aorta and the pulmonary arteries are divided to include the amount of tissue needed. If the lungs are being recovered, the left heart is vented through a broad incision in the left atrium (anterior to the left pulmonary veins). This is done before the infusion of lung preservation solution. The pulmonary veins are, in this particular instance, not divided at the pericardial reflection. Instead, the left atrium is opened and carefully transected to preserve a posterior atrial cuff around the pulmonary veins, much as in the case for cardiectomy in the recipient. The main pulmonary artery is divided before the bifurcation. The remainder of the heart recovery is as described above. The heart is removed from the operative field to a back table, where it is examined while being immersed in ice-cold saline solution. If present, a patent foramen ovale is closed. The graft is packaged in a self-sealing plastic bag containing 5 percent dextrose in normal saline solution. The packaged graft is placed in a sterile, sealed container and immersed in ice in a chest for transport. Portions of donor thymus, spleen, and hilar or mesenteric lymph nodes are obtained and stored for immunologic evaluation. Frequent communication between the recovery team and the recipient team will minimize graft cold ischemia time. It is generally recommended that graft cold ischemic time be kept less than 4 h. However, successful CT with longer cold ischemic times (up to 10.5 h) have been reported by investigators at LLU.[9]

## CARDIAC GRAFT IMPLANTATION

The biatrial technique (Fig. 89-1A) of graft implantation during CT was described by Lower and Shumway in 1967.[10] This technique may create oversized atria and may distort right atrial geometry leading to atrioventricular valve insufficiency and/or arrhythmias. Bicaval anastomosis, described by Dreyfus and colleagues,[11] is now the most commonly employed technique (Fig. 89-1B). Bicaval CT preserves right atrial morphology and is applicable at any age. It is particularly useful during reoperative CT or when space is an issue. The recipient procedure is accomplished through a median sternotomy. The thymus is excised. At LLU, the recipient is placed on cardiopulmonary bypass using aortic and right atrial cannulation. Systemic cooling to a core temperature of 18 to 20°C is utilized routinely. The aorta is cross-clamped, and when target hypothermia is achieved, bypass flow is markedly reduced, and the passive venous cannula is replaced by flexible pump suckers. The aorta and pulmonary trunk are divided. Both the SVC and the IVC are divided, preserving a small atrial cuff on each cava to facilitate anastomoses. A left atriectomy is performed, leaving a posterior atrial cuff that contains the pulmonary veins. The native heart is removed from the chest. The donor heart is evaluated, and the left atrium is trimmed to match the recipient left atrial cuff. The left atrioatrial anastomosis is performed first. A small area of the anastomosis is kept incomplete so that cold saline can be flushed intermittently through the left-sided structures. The IVC anastomosis is then completed, followed by an end-to-end anastomosis of the SVC. The passive venous cannula for cardiopulmonary bypass is inserted into the donor right atrium, via the appendage. The aortic anastomosis is completed, and intracavitary air is displaced by flushing of the left heart with cold saline. The aortic clamp is removed, ending graft cold ischemia. The pulmonary arterial anastomosis is completed during reperfusion of the allograft. All anastomoses are performed with continuous polypropylene sutures. The graft and the patient are rewarmed and reperfused for at least an hour to permit full recovery of the allograft heart. As the recipient rewarms, nitroglycerin is infused intravenously. Drugs, such as dopamine and milrinone, are infused in low dosage intravenously when the recipient reaches 34 to 36°C. The recipient is then separated from extracorporeal circulation.

A biatrial anastomosis is usually employed in neonates and very small babies. The interatrial septum is anastomosed first, followed by the right atrium and then the left atrium. The recovery and trimming of the donor heart and the techniques of CT are modified to cope with various anatomic situations, examples of which are discussed below.

### Infants Who Require Replacement/ Reconstruction of the Aortic Arch

The technique of orthotopic CT and aortic arch reconstruction is exemplified by that used for HLHS or its equivalent (Fig. 89-2) and was first described in detail in 1986 and later modified to reduce the duration of circulatory arrest.[12] The chest is opened through a midsternal incision and thymectomy is accomplished. Cardiopulmonary bypass is initiated using a single venous drainage cannula in the right atrium, and an arterial perfusion cannula that is placed in the pulmonary trunk and directed into the arterial duct. The ductus containing the arterial cannula is snared to prevent flow into the lungs. Systemic cooling to a core temperature of

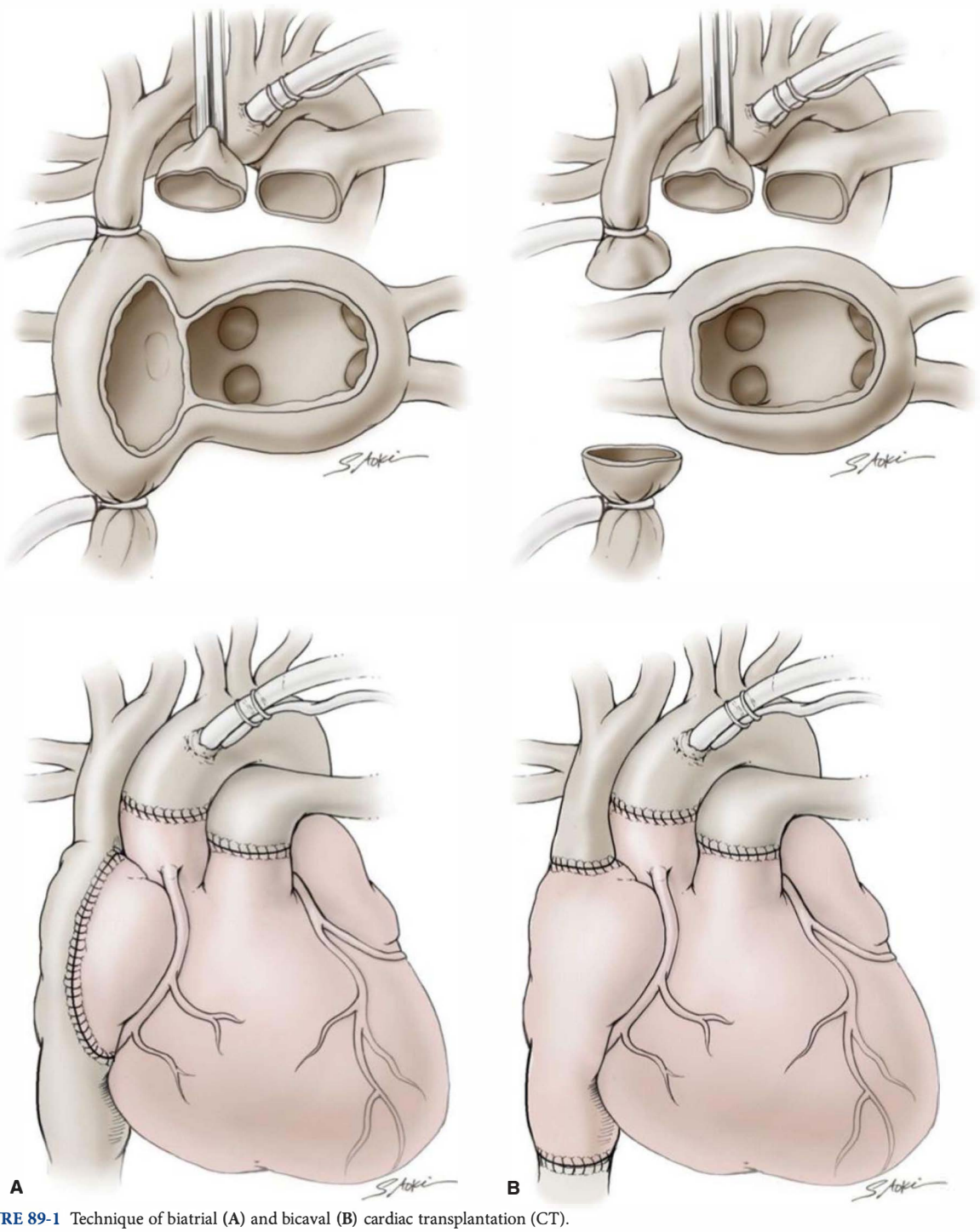



**FIGURE 89-1** Technique of biatrial **(A)** and bicaval **(B)** cardiac transplantation (CT).

18 to 20°C is achieved within 12 to 15 minutes. During this period, branches of the aortic arch are dissected and surrounded individually with loose tourniquets. The perfusion rate (or volume) is reduced to approximately 20 cc/kg/min, and thereafter varies between 10 and 30 cc/kg/min until rewarming is begun. The diminutive ascending aorta is ligated and divided just proximal to the brachiocephalic artery. Traction on this ligature facilitates exposure of the proximal descending aorta. The passive atrial drainage cannula is replaced with a flexible pump sucker. The main

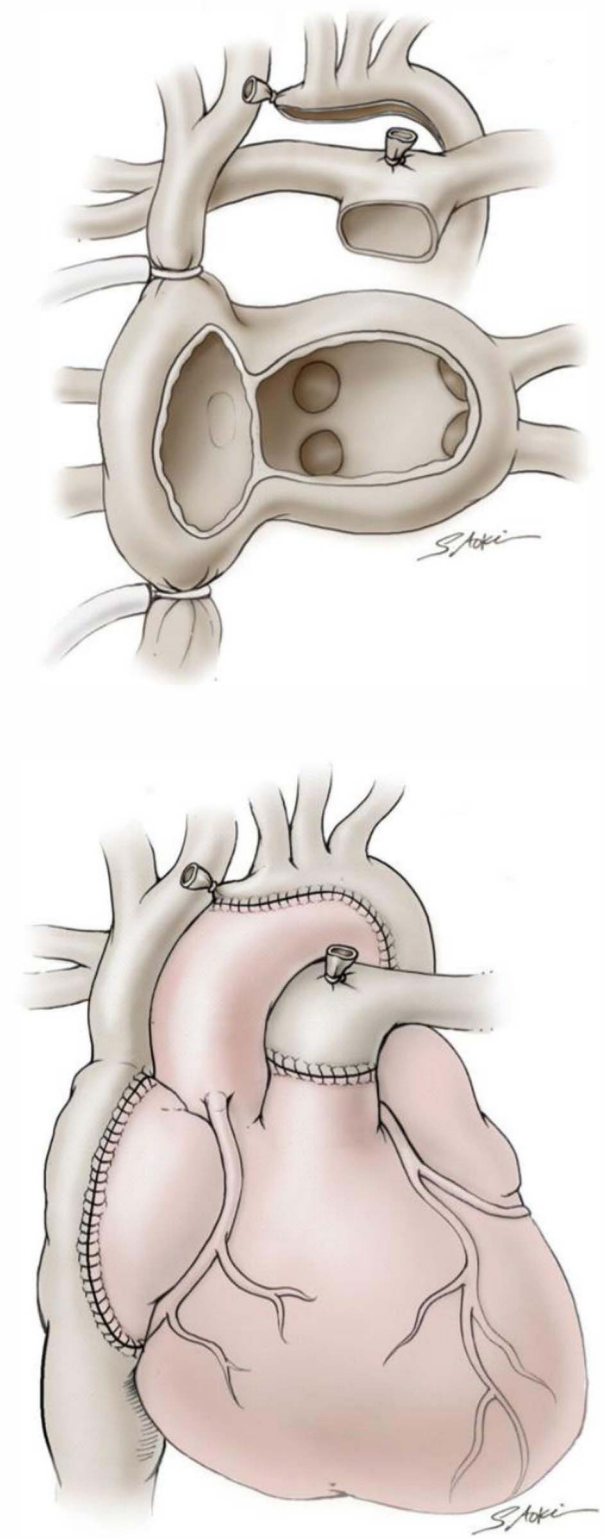


FIGURE 89-2 Cardiac transplantation of infants with hypoplastic left heart syndrome (note the technique for aortic arch reconstruction).

pulmonary artery is transected at the level of the valve. The hypoplastic heart is excised, leaving in place posterior atrial wall cuffs and a rim of atrial septum.

After inspection of the recipient's pulmonary veins, implantation of the donor heart begins with the atrial septum at its caudal aspect using a continuous monofilament suture, a portion of which is carried up the septum and around the top of the right atrium. The other portion of the same suture is used to anastomose the caudal portion of the right atrium, eventually meeting up with the segment of suture used to attach the upper portion of the atrium. A flexible suction catheter is repositioned into the right atrial appendage while the graft is retracted toward the operating surgeon and the left atrial anastomosis is initiated at its junction with the caudal septum. After half a dozen sutures, the heart graft is replaced into the remaining posterior pericardial well, and the dome of the left atrium is anastomosed toward the surgeon. Again, a small portion of the left atrial anastomosis is left incomplete so cold saline can be flushed through the left-sided structures. With the infant in Trendelenburg position, the aortic arch vessels are snared, the circulation is arrested, and the arterial perfusion cannula is withdrawn. The arterial duct is ligated and divided, and nearly all ductal tissue is excised. The undersurface of the aortic arch is incised from the level of the brachiocephalic trunk to about 1 cm down the descending aorta, beyond the ductus arteriosus. Special care is exercised to identify and avoid injury to the recurrent laryngeal and phrenic nerves. The neoaortic arch is reconstructed with the opened, long segment of donor aortic arch, starting at the descending aorta, beyond the amputated duct. Selective low-flow hypothermic cerebral perfusion may be employed here, but a period of 15 to 25 min of circulatory arrest provides an unencumbered, bloodless field for this part of the procedure, without additional neurological risk. The aorta is filled with cold saline by way of the donor brachiocephalic artery stump, which is also used for reinsertion of the arterial cannula. The passive venous cannula is placed through the appendage into the donor right atrium. Perfusion is resumed, the left atrial anastomosis is completed, and any residual air is evacuated through a vent site in the donor ascending aorta. The occluding tourniquets around the arch vessels are removed. The pulmonary arterial anastomosis is completed during the early warming phase of recirculation. The patient is gently rewarmed to 36°C, using a minimum of 60 minutes of extracorporeal reperfusion. In instances when cold graft ischemic time is markedly prolonged (as in very distant retrievals), reperfusion time may be extended to 80 or 90 minutes to achieve complete functional recovery of the heart.

## Infants Who Have Failed Norwood's Stages I or II Procedures

In this special situation, the donor heart procurement includes the central pulmonary arteries, the SVC, and the complete aortic arch. Recipient dissection exposes the aortic

arch, the aortopulmonary or cavopulmonary shunt, and both branch pulmonary arteries. The shunt is divided, the native pulmonary arterial bifurcation and central branches are replaced as necessary with donor pulmonary arteries, and the donor aorta is connected end-to-end to the previously reconstructed aortic arch. If the distal arch is obstructed, the aortic arch is completely reconstructed with donor aorta. Circulatory arrest is unnecessary in the first instance, but may be employed to enable arch reconstruction. The rest of the implantation is similar to the procedure for HLHS described previously.[13] Cavocaval anastomoses are utilized if CT follows stage II hemi-Fontan or bidirectional Glenn procedures.

## Recipients with Situs Inversus

Donor cardiectomy is performed with en bloc removal of the SVC and the innominate vein, which together are used to reconstitute cephalic venous drainage in the recipient. The donor left pulmonary vein orifices are oversewn, and the left atrium is opened vertically between the right pulmonary veins. This approach helps align the donor graft for anastomosis with the recipient right-sided pulmonary atrium. The recipient procedure is performed with low-flow hypothermic perfusion, as described above. The left pericardium, which is anterior to the phrenic nerve, is excised. The recipient heart is removed, leaving behind a small pulmonary atrial cuff and abundant systemic atrial tissue in continuity with the leftward-positioned IVC. The recipient systemic venous atrial remnant is fashioned into a short conduit in continuity with the IVC, thus directing IVC drainage toward the right side of the recipient. Graft implantation begins with the pulmonary atrial anastomosis. The IVC of the recipient, which is lengthened toward the right, is anastomosed to that of the donor heart. The recipient's pulmonary artery is opened longitudinally into the left pulmonary artery. The short stump of native main pulmonary artery is closed right-to-left with a running suture, leaving a left-sided recipient pulmonary arterial orifice, which is anastomosed to the donor main pulmonary artery. Both native recipient and donor aortas are intentionally shortened to reduce anterior bulging of the ascending aorta. The aortic anastomosis is then accomplished. Air is displaced from the left-sided structures, and low-flow hypothermic graft reperfusion is commenced. The donor SVC/innominate vein is anastomosed to a large recipient transverse brachiocephalic (innominate) vein or to the left-sided SVC, anterior to the great arteries. The passive venous cannula is inserted into the systemic atrium, and recipient and graft rewarming is begun as extracorporeal flow is gradually increased.[14] The procedure is illustrated in Figure 89-3.

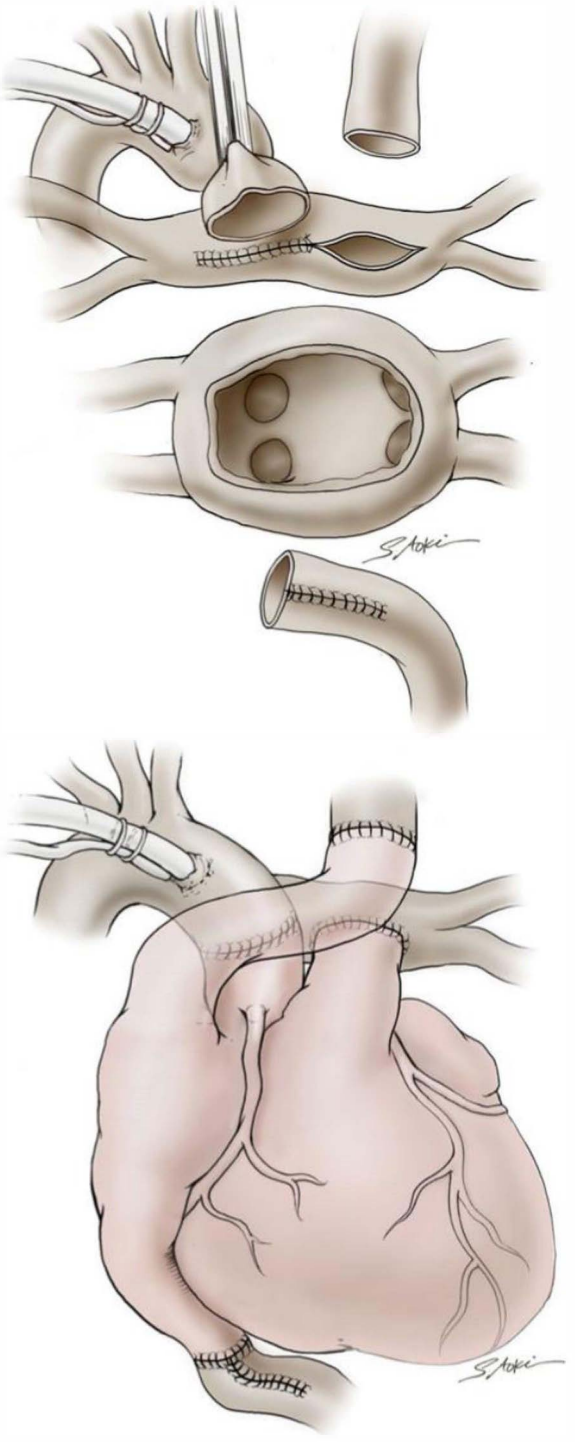


**FIGURE 89-3** Cardiac transplantation in children with situs inversus. Cardiectomy is performed, the pulmonary anastomotic site is relocated to the left, and the inferior vena cava is rerouted to the right of the midline (top). Graft implementation is performed in the usual fashion, with the donor's left brachiocephalic vein anastomosed to the left superior vena cava (bottom). The superior caval connection is positioned anterior to the shortened aorta.

## Cardiac Transplantation After a Failed Fontan Operation

Multipalliated children are always a challenge. Most have had three or more previous sternotomies, and may be nutritionally depleted following attempts to establish satisfactory

Fontan physiology. These children usually have atrial situs solitus, but may occasionally have situs ambiguous or inversus. The donor heart is recovered with adequate systemic veins and pulmonary arteries for reimplantation, using a cavo-caval strategy. Profound hypothermic cardiopulmonary bypass is established with the use of single aortic and venous cannulae, and a low-flow state is established. Using flexible "sucker" venous drainage, cardiectomy is performed. Graft implantation begins with attachment of the pulmonary atria. This is followed by anastomosis of the IVC, the main pulmonary artery (or separate right and left pulmonary arteries), one or both superior cavae or internal jugular veins and, finally, the aorta. These features are illustrated in Figure 89-4.

## SURVEILLANCE

At LLU, CT recipients are followed and evaluated by a specialized team that consists of pediatricians, coordinators, and pharmacists. Cardiologists and other pediatric subspecialists, including surgeons, act as consultants. Initially, office surveillance occurs twice weekly, then weekly, and then monthly for the first year. Follow-up visits are usually less frequent after that time. Transplant surveillance is a lifetime commitment that should prove mutually beneficial to both the recipient and the CT recipient's parents. The outpatient follow-up visits include history and physical examination, electrocardiography (ECG), echocardiography (ECHO), indicated chest roentgenograms (CXR), complete blood count, immunosuppression drug levels, measures of renal function, and viral titers. Cardiac biopsy, coronary angiography, and intravascular ultrasound (age 6 and older) are accomplished annually beyond the first posttransplant year. Testing throughout the patient's life is tailored to individual requirements and specific protocols.

## IMMUNOSUPPRESSION STRATEGIES

Immunosuppression strategies in pediatric CT are built around induction versus no induction, and double- versus triple-drug regimens. None of these strategies, however, have been evaluated in large-scale, randomized, controlled studies. Their use in pediatric CT has evolved from experience in laboratory animal models of infant CT, or has been adapted from adult thoracic and pediatric noncardiac solid organ trials. An algorithm for the management of immunosuppression is shown in Figure 89-5.

## INDUCTION

Induction therapy (the use of monoclonal or polyclonal antibody T-cell depleting agents) remains controversial. Induction was employed early in transplantation and then fell out of favor because of concerns about overimmunosuppression

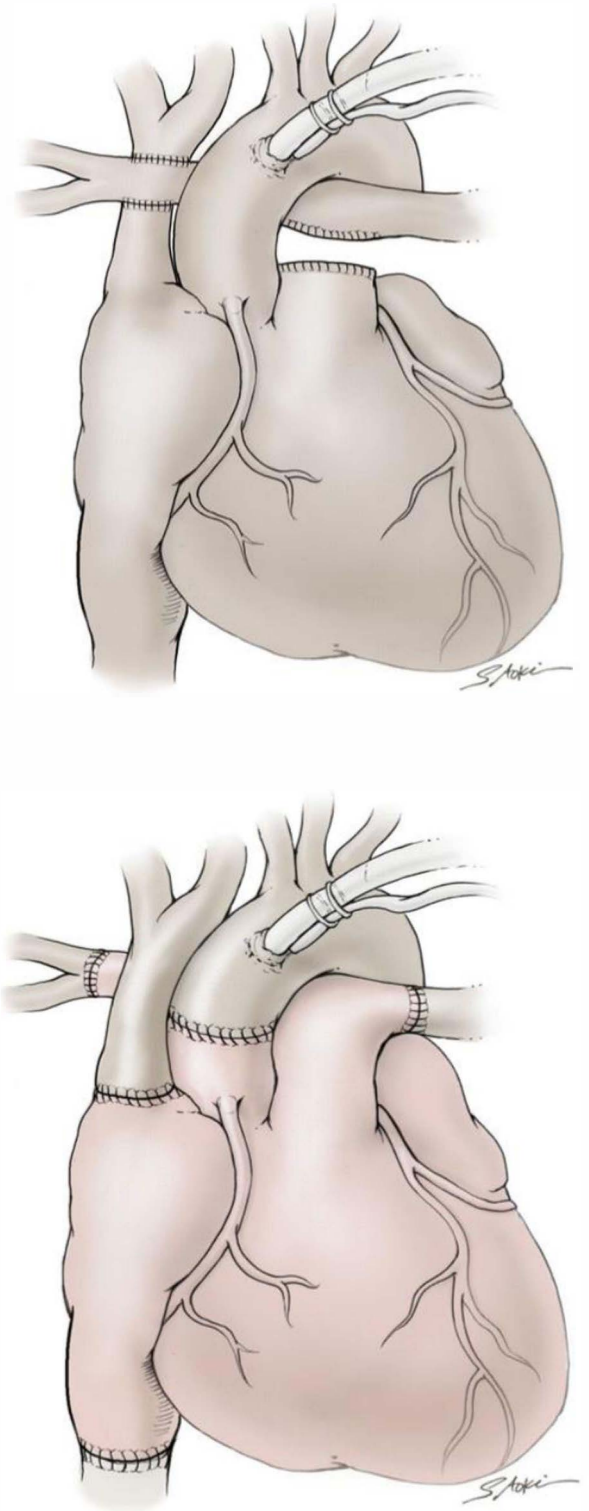


**FIGURE 89-4** Cardiac transplantation after a failed Fontan procedure (top). A cavocaval strategy is employed (bottom). On occasion, the central pulmonary arterial tree may require replacement with en bloc donor pulmonary arteries, as illustrated here.

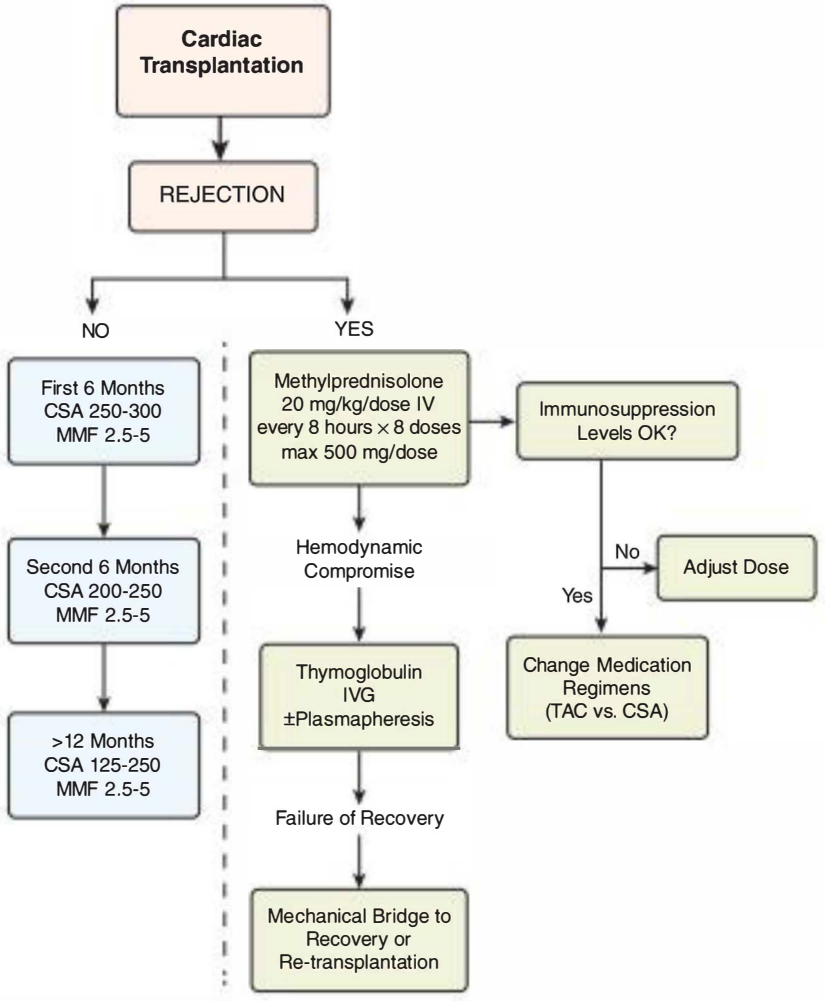



**FIGURE 89-5** Decision-making flowchart for immunosuppression management after pediatric cardiac transplantation (Loma Linda University protocol). CSA, cyclosporine trough level (ng/mL); IVG, intravenous gamma globulin; MMF, mycophenolate mofetil blood level (mycophenolic acid) (μg/mL); TAC, tacrolimus; TX, transplant.

with resultant CMV infections and the development of post-transplant lymphoproliferative disease (PTLD) associated with Epstein–Barr virus (EBV). Renewed interest in the use of induction antibody preparations occurred as a means to reduce or eliminate the need for corticosteroids. Studies have demonstrated the efficacy of this approach.[15] In the most recent report from the registry of the ISHLT,[4] 60 percent of pediatric CT patients were treated with induction agents in 2008 compared with 37 percent that were treated with induction agents in 2001. The registry data did not show a difference in rejection episodes from initial discharge to 1-year follow-up between patients with or those without induction therapy. Nor has there been an increase in the incidence of PTLD with induction. With the exception of neonates in whom induction is not used, rabbit-derived polyclonal antibody is employed in all LLU-managed pediatric recipients in a steroid-avoidance regimen.

## DOUBLE- VERSUS TRIPLE-DRUG MAINTENANCE REGIMENS

Maintenance immunosuppression is typically employed in two forms: a dual-drug regimen consisting of a calcineurin inhibitor (CNI) and a cell cycle inhibitor (CCI) versus a triple-drug regimen with a CNI, CCI, and prednisone. Although this is the typical therapy, there are many variations used in actual practice. A list of immunosuppressive agents used for induction and maintenance therapy is summarized in Table 89-5.

## CALCINEURIN INHIBITORS

Essentially, all immunoregulative regimens start with a CNI, either cyclosporine or tacrolimus. These immunosuppressive

**TABLE 89-5: Commonly Used Immunosuppressants for Cardiac Transplantation**

| Class | Mechanism | Toxicity |
|---|---|---|
| IL-2 Receptor inhibitors (Induction)<br>• Basiliximab (Simulect)<br>• Daclizumab (Senapax) | Antibodies to IL-2 receptor that block T-cell proliferation | • No toxicity |
| Polyclonal antibodies (Induction)<br>• Antithymocyte globulin (ATG) | Nonspecific lysis and clearance of coated B and T cells | • Viral infection<br>• Serum sickness |
| Calcineurin inhibitors<br>• Cyclosporine (Neoral)<br>• Tacrolimus (Prograf) | Blocks IL-2 production via activated T-cells; decreases cellular proliferation | • Neurotoxicity<br>• Nephrotoxicity<br>• Diabetes<br>• Hirsutism |
| Antimetabolites<br>• Azathioprine (Imuran)<br>• Mycophenolate Mofetil (Cellcept) | Inhibits DNA synthesis by interrupting purine synthesis | • Leukopenia<br>• Anemia<br>• Diarrhea |
| Regulatory kinase inhibitor<br>• Everolimus (Zortress)<br>• Sirolimus (Rapamune) | Inhibits TOR protein causing arrest of cell cycle in G1 phase | • Hypercholesterolemia<br>• Hypertriglyceridemia<br>• Impaired wound healing |
| Steroids<br>• Prednisone | Blocks cytokine production | • Hypertension<br>• Impaired wound healing<br>• Osteonecrosis<br>• Weight gain |

Data from Baker TB, Axelrod D. Transplantation. In: Makary MA (ed). *General Surgery Review*. Washington, DC: Ladner-Drysdale, 2004:302.[30]

agents target T-lymphocytes and inhibit their activation in response to alloantigen stimulation. Calcineurin-inhibitors block IL-2 gene expression and the production by activated T-cells. In the ISHLT registry report, the use of tacrolimus 1 year after transplantation surpasses the use of cyclosporine 58 to 38 percent. The main advantage of tacrolimus is its reduced cosmetic (e.g., hirsutism and gingival hyperplasia) side effects. It is 100 times more potent than cyclosporine, and is used successfully in patients with recurrent rejection who cannot be controlled with cyclosporine. There are real concerns, however, about an increased incidence of PTLD and posttransplant diabetes among recipients managed with tacrolimus. Newer strategies that use lower target blood levels of tacrolimus have helped ameliorate both of these concerns. Interestingly, long-term survival tends to favor the maintenance use of cyclosporine, but does not establish cause and effect.

Cyclosporine has been the preferred CNI at LLU. Target trough levels (whole blood monoclonal assay) are 250 to 300 ng/mL for the first 6 months, 200 to 250 ng/mL for the next 6 months, and 125 to 150 ng/mL thereafter if the rejection history is acceptable. Tacrolimus is used primarily in selected situations such as high-risk candidates (multiple prior cardiac surgeries), high recipient panel-reactive antibody, and/or African American recipients. Tacrolimus is also used in patients with recalcitrant rejection, after retransplantation, and among children for whom cosmetic side effects (with the use of cyclosporine) become seriously problematic.

## CELL CYCLE INHIBITORS

There are two main categories of CCIs (also known as antiproliferative agents). They are antimetabolites and regulatory kinase inhibitors. Antimetabolites, such as azathioprine (AZA) and the more recent mycophenolate mofetil (MMF), function by blocking purine synthesis. Production of DNA is blocked; hence, the normal cell cycle is arrested. Historically, AZA has been the drug of choice in this class of immunosuppressants. However, ISHLT registry data suggest MMF is now used in 60 percent of pediatric CT recipients (at the 1-year follow-up) instead of AZA. Studies in children have indicated that potential benefit can result from the use of MMF.[16,17] Decreased risk of rejection, decreased cardiac allograft vasculopathy (CAV), and improved survival have been observed with its use.[18] MMF may also decrease the progression of coronary intimal thickening.[19] Like AZA, MMF can produce bone marrow suppression. Significant gastrointestinal side effects may occur with the use of MMF, limiting patient tolerability. The primary immunoregulation protocol at LLU utilizes MMF in a dose of 600 mg/m$^2$/day divided twice daily, advancing the dose as tolerated to maintain a blood level of 2.5 to 5.0 µg/mL (measuring mycophenolic acid levels).

Regulatory kinase inhibitors cause cellular arrest at the G1-stage of the cell cycle by inhibiting the TOR protein. The regulatory kinase (or M-TOR) inhibitors currently used for immunosuppressive therapy in pediatric CT are sirolimus and everolimus. They each function

synergistically with CNI, and have been found useful in the management of rejection, and in the reduction of renal dysfunction and other side effects of CNIs.[20] Sirolimus is employed at LLU for recurrent rejection, in conjunction with MMF (to decrease or eliminate calcineurin use) in children with renal insufficiency, as solo therapy after treatment for PTLD, and in children who have evidence of moderate-to-severe CAV.

## CORTICOSTEROIDS

Oral prednisone has been a historic mainstay of rejection prophylaxis in pediatric CT. The ISHLT registry data show that 55 percent of patients are still being treated with prednisone at 1 year post CT. Nevertheless, experience indicates that effective rejection prophylaxis in pediatric CT recipients can be achieved without the use of maintenance prednisone therapy. Indeed, ISHLT registry data reveal that prednisone usage falls to 38 percent by the fifth posttransplant year. Some believe steroid avoidance requires antibody induction therapy. However, the use of newer immunosuppressive agents has paved the way for prednisone reduction or elimination regardless of the use of an induction antibody. Programs that use maintenance prednisone typically start at a dose of 2 mg/kg per day and wean over the first 3 months to a maintenance dose of 0.1 to 0.3 mg/kg once per day or every other day.

Steroid avoidance has been practiced at LLU from the inception of the program. Oral prednisone may be used temporarily in the treatment of rejection or chronically in the very few children in whom no other combination of agents is effective or tolerated.

## NONPHARMACOLOGIC ANTIREJECTION MEASURES

Three other therapies may play a role in pediatric CT. Total lymphoid irradiation has been used in the treatment of recalcitrant rejection.[21] It has become less important; however, with the availability of newer immunosuppressive agents. Plasmapheresis has been used[22] either before CT (in highly sensitized patients) or in posttransplant recipients who experience acute antibody-mediated rejection (AMR) or in whom AMR is anticipated. Another measure, photopheresis, involves the extraction of lymphocytes from recipients. The lymphocytes are pretreated with psoralen, exposed to ultraviolet A light, and reinfused into the recipient. Photopheresis has been helpful in the prevention[23] and treatment of recurrent rejection in adults, but there are no published reports of its efficacy in children.

## DIAGNOSIS OF ALLOGRAFT REJECTION

A noninvasive strategy is utilized to diagnose graft rejection among infants less than 2 years of age. This approach consists of frequent and thorough examinations. Office evaluation is coupled with diagnostic testing that includes CXR, ECG, and ECHO. Changes in shape and size of the cardiac silhouette and the presence or absence of pulmonary infiltrates on CXR provide clues to the possibility of graft rejection or pulmonary infection. Serial CXR comparisons will identify subtle, and perhaps earlier, changes. Obvious CXR changes imply a late diagnosis of rejection.

The ECG is of questionable value in the early diagnosis of graft rejection, although a >20 percent decrease in combined voltage is suspicious of allograft edema caused by the rejection process. Such a dramatic fall in ECG combined voltage simply adds one bit of data to the noninvasive rejection diagnosis algorithm.

Serial ECHO is a powerful tool for the diagnosis of graft rejection. In general, overall subjective impression is of immense value, but objective findings are just as important. Findings include an increase in ventricular wall thickness, a loss of diastolic compliance, a fall in systolic markers (percent shortening fraction and ejection fraction), new atrioventricular valve regurgitation, and a new pericardial effusion. The more of these findings that are present, the more certain the diagnosis of rejection, particularly if they occur between 3 weeks and 3 months after CT when graft rejection is more commonly encountered.

Older, larger infants, children, and adolescents are subjected to regularly scheduled weekly endomyocardial biopsies until two consecutive biopsies are free of microscopic rejection. Additional biopsies are largely confirmatory in nature, and are tailored to individual recipient requirements.

The risk of graft rejection is being explored through molecular expression testing among adult recipients of cardiac allografts. This methodology has not yet proven to be of value in the anticipation of graft rejection in infants and children.

## TREATMENT OF ACUTE REJECTION

Treatment of a first-time acute graft rejection episode involves high-dose intravenous or oral administration of corticosteroids. Intravenous treatment is often followed by the use of oral prednisone, which is tapered gradually to discontinuation over several weeks. Acute rejection in LLU infants and children is treated with intravenous methylprednisolone in a dose of 20 mg/kg per dose to a maximum of 500 mg per dose twice per day for eight doses. Uncomplicated rejection that is diagnosed by biopsy alone may be treated with oral prednisone 2 mg/kg per day for 3 days, with a taper to 0 over 3 weeks. Patients with recurrent rejection or with acute rejection manifested by hemodynamic compromise are managed in the pediatric intensive care unit with the use of anti-T-cell antibodies (monoclonal or polyclonal) in addition to corticosteroids. At LLU, antithymocyte globulin (ATG) in a dose of 1.5 mg/kg per day is administered intravenously over 6 hours. The dose is repeated daily for 7 to 10 days. A lymphocyte profile is obtained on day 3, targeting an absolute CD3 count of less than 200 cells per mL. Intravenous

immunoglobulin, administered in relatively high doses, may also be useful in the management of acute rejection.

The etiology of acute graft rejection requires investigation, especially if occurring late after CT (>3 months). If immunosuppressive doses have been administered faithfully, and if the desired therapeutic levels have been maintained, the desired level should be increased or the agent should be changed. Noncompliance must be suspected in any late rejection episode, especially among recipients with low drug levels and among adolescents.

## COMPLICATIONS

The most important untoward early consequences of CT are rejection and infection. Other early complications are largely drug side effects or toxicities, and they include hypertension, seizure, renal dysfunction, hematologic abnormality, and hepatic dysfunction. Late complications include chronic rejection, neurodevelopmental delay, CAV, chronic renal failure, and PTLD. Leading causes of late mortality include CAV, chronic graft dysfunction, and malignancies.

## CARDIAC ALLOGRAFT VASCULOPATHY

CAV is a major issue, resulting in increased morbidity and mortality. It probably represents subclinical chronic graft rejection and, as such, may be preventable or even reversible with current drug management. The reported prevalence in pediatric CT ranges between 25 and 45 percent, with the lowest prevalence among recipients who are <10 years old when they have CT. Thus far, the prevalence of this phenomenon appears to be lower among pediatric recipients than it is in the adult population. The most important risk factor associated with increased CAV is increased frequency and severity of graft rejection.[24] Prevention of CAV includes the use of increased immunosuppression, calcium channel blockers, and lipid-lowering agents. As previously mentioned, regulatory kinase inhibitors have been shown to reduce the development of CAV, but whether this translates into improved long-term outcomes has yet to be determined. Treatment of severe, established CAV is elective retransplantation.

## RETRANSPLANTATION

Retransplantation accounts for 5 percent of all pediatric CT, and will certainly increase in use over time. Indications for retransplantation include primary graft failure, irreversible acute rejection, chronic graft dysfunction and advanced CAV.

## OUTCOMES AND THE LOMA LINDA UNIVERSITY EXPERIENCE

Data from the Pediatric Heart Transplant Study (PHTS) Registry, gathered since 1982, show an overall actuarial survival at 10 years of 66 percent in all pediatric age groups (Fig. 89-6).[25] Allograft rejection has been the primary cause of death during the first 3 posttransplant years and CAV is the major cause of late mortality.

Since 1985, 474 infants and children under 18 years of age have been recipients of CT at LLU. The majority ($n$ = 315) of the recipients have been under 12 months of age. Overall actuarial survival, including operative mortality, at 10 years is 66 percent. Three-quarters of newborn recipients are expected to be alive at 10 years. There is a 79 percent incidence of freedom from CAV at 10 years in our patient population.

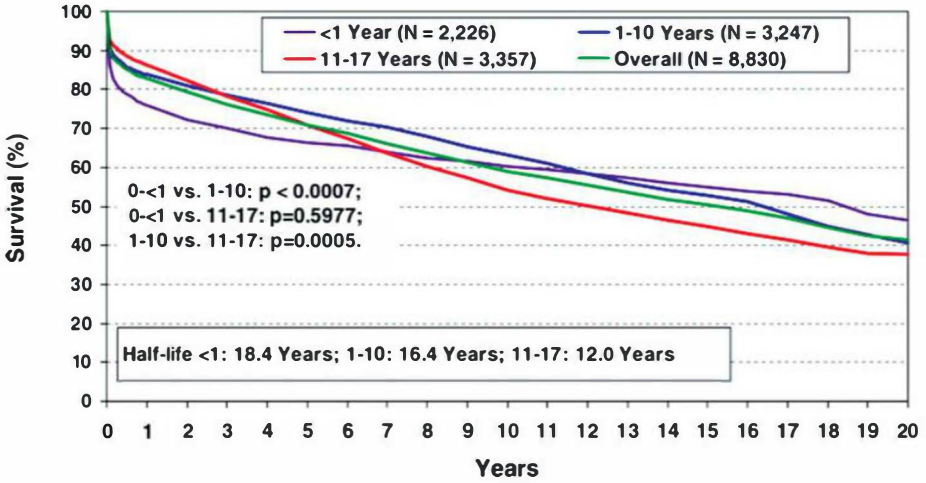



**FIGURE 89-6** Actuarial survival of 537 pediatric patients, stratified by age (January 1982–June 2009). (Reproduced with permission from Kirk R, Edwards LB, Kucheryavaya MS, et al. The registry of the international society for heart and lung transplantation: fourteenth pediatric heart transplantation report—2011. *J Heart Lung Transplant*. 2011;30(10):1095-1103.)

The incidence of freedom from posttransplant malignancy is 89.7 percent at 10 years with the most common malignancy being lymphoproliferative disease. As mentioned above, the first survivor of neonatal transplantation celebrated his 27th birthday with his original allograft in November 2012.

The availability of donor organs remains a challenge, particularly for recipients in very early life. Hence, biological replacement of the heart will continue to be reserved for infants and children who have no other option. Today, for example, just a few young infants with HLHS are ever considered for CT. They fall into two categories: (1) those for whom palliative intervention is judged unlikely to succeed and (2) those who fail to respond favorably to initial palliative reconstruction. Outcomes probably will reflect the nature of this strategy in managing infants with HLHS when compared with elective primary transplantation. A total of 157 HLHS patients have received CT at LLU since the program inception in 1985, but only 5 HLHS patients have been transplanted in the last 5 years. Among this cohort, operative mortality has been 11.5 percent (18/157) and 12-month actuarial survival has been 82.7 percent.

## FUTURE TRENDS

The relatively fixed number of donors for pediatric recipients requires that their distribution and utilization be maximized. Hence, distribution policies have been developed to ensure that adolescent organs reach pediatric recipients preferentially. In addition, a protocol has been devised for the use of ABO-mismatched hearts in young infant recipients.[26] The outcomes of this approach have been excellent, mortality among infants waiting for transplantation has been reduced, and fewer donor hearts have been wasted in this age group. Still, only two-thirds of potential North American pediatric donor hearts are utilized.[27] Strategies to use more of these donor organs should be evaluated. Heart grafts from non–heart-beating donors are a potential resource. The Denver Children's Hospital group reported three successful infant CTs using non–heart-beating donors.[28] Their particular protocol created some debate, but a variation of the protocol that includes a longer waiting period between cessation of cardiac function and donor heart recovery should succeed in increasing the donor organ supply.

As the requirement for CT among young infants with HLHS and its equivalent has diminished, there has been an increasing number of children and adolescents with end-stage congenital heart disease for whom transplantation is the only route to survival. In addition, the demand for retransplantation is on the rise. VADs and perhaps innovative ventricular remodeling procedures will play a more prominent role in bridging these children to transplantation.

Finally, the future ability to induce graft-specific tolerance will make organ transplantation an exceedingly attractive therapy. Indications for pediatric CT will expand, as will the demand for donor organs, including organs from other species. Some of today's most promising research in xenotransplantation is focused on a tolerance model. Together, tolerance induction and xenografting may become the future of pediatric CT.

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## PEDIATRIC CARDIAC TRANSPLANTATION BOARD REVIEW QUESTIONS (CHAPTER 89)

1. CNI toxicity profile includes all of the following, except
   A. Diabetes
   B. Hirsutism
   C. Leukopenia
   D. Neurotoxicity
   E. Nephrotoxicity

2. True or False: Complex congenital heart disease has been the most common indication for heart transplantation in infants who are less than 12 months of age.

3. Prevention of CAV includes the use of all the following, except
   A. Immunosuppression
   B. ACE inhibitors
   C. Calcium channel blocker
   D. Lipid lowering agents
   E. Regulatory kinase inhibitors

4. The following pediatric indications for orthotopic CT are correct, except
   A. A child with protein-losing enteropathy following a Fontan operation.
   B. A 2-month-old infant with multiple large cardiac rhabdomyomas, incessant ventricular tachycardia, and pulmonary hypertension.
   C. A young adult who had CT during early infancy and now has grade 3–4 CAV.
   D. A 14-year-old girl whose history includes a Ross–Konno procedure and mitral valve replacement. She now has end-stage cardiomyopathy and pulmonary vascular resistance of 8 Woods units; unresponsive to pulmonary vasodilators.

5. CNI mechanism of action consists of
   A. Inhibits TOR protein causing arrest of cell cycle in G1 phase
   B. Inhibits DNA synthesis by interrupting purine synthesis
   C. Antibodies to IL-2 receptor that block T-cell proliferation
   D. Blocks IL-2 production via activated T cells
   E. Blocks cytokine production

## ANSWERS

1. **Answer: C.** (Found in Table 89-5.)
2. **Answer: True.** (Found in Indications section.)
3. **Answer: B.** (Found in CAV section.)
4. **Answer: D.** (Found in Contraindications section.)
5. **Answer: D.** (Found in Table 89-5.)

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# Management of Adults with Congenital Heart Disease

*Kaushik Mandal*
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The extraordinary advances and dramatic successes of pediatric cardiology and surgery over the past 50 years have witnessed an increase in children born with congenital heart disease (CHD) who survive into adulthood. This success in survival has created a new population of patients of adults with congenital heart disease (ACHD). The number of ACHD will very likely continue to increase in the near future.[1] The 32nd Bethesda Conference had estimated that there were approximately 800,000 adults with CHD in the United States in the year 2000[2]; in the United Kingdom alone there are currently approximately 250,000 ACHD patients.[3]

Since about 0.8 percent of live births are complicated by cardiovascular malformations (disregarding the two most common congenital cardiac anomalies: functionally normal congenital bicuspid aortic valve and mitral valve prolapse), approximately 2800 adults per million population will have some form of CHD, with half of them having moderate- or high-complexity defects.[2] These patients are at significant risk of early mortality from complications of future treatment including reoperation, especially if undertaken in facilities or by physicians not resourced or trained in their care. At present, there is shortage of facilities dedicated to the care of adults with CHD.[4] Care givers and ACHD should have been taught in adolescence about their condition, their future outlook, and the possibility of further surgery and complications, as appropriate. They should be advised about their responsibility in ensuring self-care and professional surveillance. Copies of operative reports should accompany patients being transferred for adult care, along with other key documents from pediatric medical records. Recommendations on transfer of care, organization of ACHD service network, infrastructural requirements, involvement of multidisciplinary teams and their training/certification have been dealt with in detail in the ESC[5] and ACC/AHA[6] taskforce guidelines. A well-working network of specialist centers with general adult care is of paramount importance since, although complex defects can be easily recognized and assigned to high-level care, even simple defects may still require specialist care under certain circumstances [i.e., atrial septal defects (ASD) in the setting of pulmonary hypertension (PAH)].

The subsequent sections of this chapter deal with clinical management of ACHD patients, with special emphasis on issues unique to each lesion, in line with the recently published ESC-2010[7] and ACC/AHA-2008[6] taskforce guidelines.

## CLINICAL EVALUATION

A detailed history from an ACHD patient aims at analyzing present and past symptoms including any significant intercurrent event. Changes in lifestyle should be recorded. Clinical examination during initial and follow-up visits should lay special emphasis on any changes in oxygen saturations, auscultatory findings, blood pressure measurements or signs of heart failure development. A 12-lead electrocardiography (ECG) and pulse oximetry should be part of the examination. Chest x-ray is performed if the clinical situation demands, and provides useful information on changes in heart size, configuration, and pulmonary vascularity.

Noninvasive investigative modalities like echocardiography, cardiac MRI (CMR) are being increasingly used for delineating the anatomy and pathophysiology in ACHD patients in preference to invasive angiographic techniques. Evaluation of arrhythmias with Holter monitoring, event recorders and detailed electrophysiological testing makes management more objective. Cardiopulmonary exercises testing (CPET) has also been gaining popularity in the assessment and follow-up of ACHD patients, especially in deciding about timing of interventions.

### Echocardiography

Echocardiography remains the first line investigation, and 2D transthoracic echo is an essential tool to objectively document the findings after a thorough clinical evaluation.

Recent developments in the field of echocardiography like 3D echo, Doppler tissue imaging, strain rate imaging, contrast echocardiography, and perfusion imaging have significantly improved its ability of functional and anatomical lesion assessment. Transesophageal echo (TEE), with its superior image quality is a useful adjunct; however, supplants 2D echo only in minority of situations like echo guided ASD closure, percutaneous valve implantations etc. It remains a versatile tool for guiding a surgeon during repair of complex pathologies; confirmation of repair quality by intraoperative TEE is a standard of care.

Echocardiography provides information on basic anatomy including cardiac position and orientation, venous return, atrioventricular and ventriculoarterial concordance. It allows evaluation of cardiac chamber morphology, ventricular function, morphology, and function of valves and detection and evaluation of shunt lesions. Echocardiographic distinction between ventricular volume overload (increased end-diastolic volume and stroke volume) and pressure overload (hypertrophy, increase in ventricular pressure) is of crucial importance in deciding the timing of intervention. Doppler echocardiography provides useful hemodynamic information such as gradients across obstructive lesions, right ventricular (RV) pressure, pulmonary artery (PA) pressure, and flow velocities.

Despite its versatility, echocardiography still remains a highly user-dependent investigation that requires special expertise for ACHD patients. Evaluation of ventricular volumes and function may be complicated by geometry and regional incoordination especially in systemic and nonsystemic RV and single ventricle pathologies. Doppler gradients may be misleading when two or more stenotic lesions lie in series. Venous return and great arteries may be difficult to image. Echocardiography is, however, the first line investigative modality, while further noninvasive imaging and invasive hemodynamic assessment are considered to supplement information missing after echocardiographic assessment.

## Cardiac Magnetic Resonance Imaging

CMR is an essential tool in the assessment of ACHD patients. It allows 3D anatomical reconstruction, not restricted by body habitus and acoustic windows and has an excellent spatial and temporal resolution. It is of immense value in volumetric assessment, anatomical delineation of great vessels and detection of myocardial fibrosis.

CMR is an alternative to echo and can provide all the information obtained by echo. Echo, however, is superior to CMR in estimating gradients, PA pressure and detecting small mobile vegetations. CMR can add value to the diagnostic work-up when echo measurements are ambiguous, e.g., ventricular volume, ejection fraction measurement and quantification of valve regurgitant fraction and help in deciding about timing of valve-related surgery.

CMR is superior and should be performed in preference to echocardiography[8] for: (1) quantification of RV volume/ejection fraction in tetralogy of Fallot (ToF); (2) evaluation of RV outflow tract obstruction (RVOTO) and RV–PA conduits; (3) quantification of pulmonary regurgitation; (4) evaluation of PA and aortic pathologies (Fig. 90-1); (5) evaluation of systemic and pulmonary venous anomalies/obstructions; (6) collaterals and arteriovenous malformations; (7) quantification of myocardial mass; (8) evaluation of myocardial fibrosis with gadolinium late enhancement and (9) tissue characterization (fibrosis/iron/adipose tissue). Patients with permanent pacemakers/defibrillators and those who are severely claustrophobic cannot be imaged with CMR; high-resolution spiral computed tomography (CT) provides in these cases a valid alternative, albeit in the setting of increased radiation exposure.

## Computed Tomography

CT plays an ever increasing role in the evaluation of ACHD patients in view of its excellent spatial resolution, ECG-gated image acquisition and rapid scanning with use of newer rotational techniques. It is particularly suited and is superior to CMR for imaging epicardial coronary arteries, collaterals



**FIGURE 90-1** Magnetic resonance imaging in an adult with severe aortic coarctation.

and for evaluating parenchymal lung disease. Its major drawback is its high dose of ionizing radiation, which makes it unattractive for serial evaluations.

## Cardiac Catheterization

Cardiac catheterization is now reserved for resolution of specific anatomical and physiological questions or for therapeutic intervention. Continuing indications include evaluation of pulmonary vascular resistance (PVR), left ventricular (LV) and RV diastolic function, pressure gradients, and shunt quantification, evaluation of aortopulmonary collaterals especially when noninvasive modalities are equivocal.

Accurate measurement of PVR in patients with shunt lesions is crucial for therapeutic decision making. Estimation of PVR requires accurate calculation of pulmonary flow, often difficult to ascertain with echo in patients with complex CHD. Measurement of oxygen uptake rather than estimation is required when the reversibility of PAH would determine the optimal treatment. Preoperative coronary angiography should be performed in men above the age of 40 years, postmenopausal women and patients with family history of or risk factors for coronary artery disease (CAD).

## Cardiopulmonary Exercise Testing

CPET including assessment of objective exercise capacity ($VO_2$ max), ventilation efficiency ($VE/VCO_2$ slope), chronotropic and blood pressure response, and exercise-induced arrhythmias give a broader evaluation of function and fitness and has end points which correlate well with mortality and morbidity in ACHD patients.[9] Serial exercise testing should be an integral part of long-term follow-up protocols and intervention trials in these patients, and has an important role in determining the timing of reinterventions.

# TREATMENT CONSIDERATIONS

Medical management in ACHD patients with heart failure, arrhythmias, pulmonary and systemic hypertension is largely supportive. Prevention of thromboembolic events and endocarditis require appropriate prophylactic measures to be instituted at appropriate times and when significant residual structural abnormalities need reintervention.

## Heart Failure

Congestive heart failure (CHF) is a common problem in ACHD patients. Specialists caring ACHD patients should follow current guidelines.[10] However, given the contrasting and different pathophysiological mechanisms at work in this group of patients, direct extrapolation of results from published studies to ACHD patients may be difficult; this is particularly true for patients with atrial switch repair for transposition of great arteries (TGA) or those with Fontan circulation. The relative lack of published data for these patients makes it difficult to specify the management of heart failure in this group of patients. Cardiac resynchronization therapy (CRT) has gained increasing interest recently in a specific subset of ACHD patients with CHF; however, objective indications for use and outcome measures are at present not clear.

## Arrhythmias and Sudden Cardiac Death

Arrhythmias are one of the most important causes for hospitalization and morbidity and mortality in ACHD patients. Risk stratification, investigation, and management algorithms are often different from those with acquired heart disease with structurally normal hearts.[11] Moreover, the onset of arrhythmia may herald hemodynamic decompensation, with amplified detrimental effects in the presence of an abnormal circulatory physiology. Results of catheter ablation are generally unpredictable in ACHD patients compared to those with ischemic heart disease. Technological improvements, however, allow consideration of catheter ablation for tachyarrhythmias for documented indications in a center with specific expertise. Antiarrhythmic drug therapy with its antecedent negative inotropic effect is poorly tolerated and there are limited data on its long-term safety and efficacy.

Sudden cardiac death (SCD) is of particular concern in ACHD patients. Five defects with greatest risk of late SCD are ToF, TGA, ccTGA, aortic stenosis (AS), and single ventricle lesions.[12,13] Unexplained syncope is alarming. Current guidelines[13] for prevention of SCD in ACHD patients recommend as follows:

- AICD implantation is indicated in survivors of cardiac arrest after exclusion of reversible causes (level of evidence IB).
- Patients with spontaneous sustained ventricular tachycardia (VT) should undergo invasive hemodynamic and electrophysiology (EP) evaluation. Recommended therapy includes catheter or surgical ablation as deemed appropriate and, if this is not successful, ICD implantation should be considered (level of evidence IC).
- Invasive hemodynamic and EP evaluation is reasonable in patients with unexplained syncope and impaired ventricular function. In absence of defined, reversible cause, ICD implantation is reasonable (level of evidence IIaB).
- EP testing may be considered for patients with recurring ventricular couplets or nonsustained VT to determine the risk of sustained VT (level of evidence IIbC).
- Prophylactic antiarrhythmic therapy is not indicated for asymptomatic patients with isolated premature ventricular contractions (level of evidence IIIC).

## Surgical Treatment

Many ACHD patients will have undergone surgery in childhood, but reintervention during adulthood may be required

for: (1) patients with prior repair with new and/or residual hemodynamic complications; (2) patients with conditions not diagnosed during childhood; (3) patients with palliative procedures; and (4) rarely, patients who have not been offered surgery due to the lack of expertise at the time the diagnosis was initially made.

ACHD patients requiring surgery have to be assessed and managed quite differently from those undergoing cardiac surgery for other acquired pathologies. Therefore, it is vital to concentrate all resources into a specialist unit for both treatment and training.[5] Even noncardiac surgery may carry a high risk in this particular group of patients, and appropriate consultation from specialists should be sought; careful preoperative planning and intraoperative monitoring are vital to ensuring a successful outcome.

One of the most challenging surgical issues in ACHD patients is heart and heart–lung transplantation. Risk-stratification scores are available for terminal CHF but may not correctly apply to ACHD patients, making decisions regarding timing of transplantation difficult. In addition to the standard pretransplant work-up, specific issues in ACHD patients are: (1) sensitization from previous transfusions that increases the risk of rejection. Treatment to reduce HLA antibody levels may be needed prior to transplant. (2) The assessment of PVR is difficult in patients with low cardiac output, residual lesions, and shunts/collaterals and has direct outcome on early graft function. (3) Detailed planning of surgical approach is crucial in many complex lesions and all anatomic details, including systemic and pulmonary venous returns that need to be defined. (4) Nonadherence to post-transplant medications is a major problem in young adults, and preexisting psychosocial issues require thorough evaluation before listing. (5) Issues that are specific to patients with Fontan circulation such as protein-losing enteropathy (PLE) and pulmonary arteriovenous malformations need to be accounted for and treated if possible before listing. (6) An increasing number of patients with end-stage cardiopulmonary lesions have underlying chromosomal anomalies which further complicate decision making. (7) Surgical issues in previously operated patients include difficulties during reentry, dissection, cannulation, bleeding, longer bypass, all of which have the potential to raise pulmonary arterial pressure (PAP) and jeopardize right heart function following engraftment. Additional point to consider during procurement for ACHD patients is to harvest extra length of vessels/pericardium for reconstruction.

As per the 2008 UNOS report 1-, 5- and 10-year survival after heart transplantation in non-ACHD patients is 88, 74 and 55 percent. For heart–lung transplantation survival is similar at 71, 50, and 30 percent. Survival after transplantation in ACHD patients is significantly lower, primarily due to higher early attrition.[14] Late attrition after transplantation has not improved significantly in the last 10 to 20 years despite introduction of newer immunosuppressants. The increasing donor shortage and inferior results in ACHD patients may influence organ allocation, strongly penalizing this particular population of recipients. Alternatives, such as long-term mechanical support and/or xenotransplantation will therefore remain important areas of research.

### Catheter Intervention

There has been a marked increase in the number and range of interventional catheterization procedures in ACHD patients, sometimes obviating the need for surgery and, in other cases, facilitating surgical intervention by the intraoperative deployment of stents (hybrid approach). Newer techniques include stenting of systemic or pulmonary vessels and percutaneous valve implantation. The decision to perform an intervention should involve a process of rigorous peer review and multidisciplinary discussion, as currently limited data exist to demonstrate noninferiority over surgery for many of these approaches.

## INFECTIVE ENDOCARDITIS

Infective endocarditis (IE) risk in ACHD patients is substantially higher than in the general population, with marked variation between lesions. It has been emphasized that good oral hygiene and regular dental care and evaluation have an essential role in reducing the risk of IE. Aseptic measures are mandatory during manipulation of venous catheters and during invasive procedures. ACHD patients should be discouraged from getting piercings and tattoos.

Current recommendations for antibiotic prophylaxis for prevention of endocarditis in ACHD patients are as follows: (1) patients with a prosthetic valve/material used for cardiac valve repair; (2) patients with previous IE; and (3) CHD patients prior to repair, if they are cyanotic or post repair with residual shunts. These recommendations are limited to dental procedures only, and are not always advocated for respiratory, gastrointestinal, genitourinary, dermatological or musculoskeletal procedures especially in absence of preexisting infections.

## NONCARDIAC ISSUES

ACHD patients are confronted with various challenges aside from their cardiac issues. These include interventions/surgery for noncardiac problems, ability to participate in exercise and sports, psychosocial issues, obtaining/maintaining employment as well as health and life insurance and finally contraception and pregnancy. Multidisciplinary teams caring for these patients need to be aware of these issues and to have established protocols for assisting them into a meaningful social life. Initiation of discussions on the issues mentioned above between treating physicians, family, and the patient needs to start as soon as the decision of transferring the ongoing care from pediatric to ACHD service is made; this process needs to be gradual and comprehensive. We will briefly touch upon these issues; a detailed discussion of

these problems can be found in the ACC/AHA-2008[6] and ESC-2003[5] taskforce guidelines.

## Exercise and Sports

Counseling for participation in sports and exercise needs to be individualized for each patient based on their ability and the impact on underlying hemodynamics and risk of arrhythmias and acute decompensation. Formal testing is of great value in mitigating the fear of physicians and their patients. Participation in regular exercise has well-documented benefits for fitness, psychological well-being, social interaction, and reduction of future risk of developing atherosclerotic disease. In general, dynamic exercise (i.e., running) is safer than static exercise (i.e., weight lifting). Risk of SCD in patients with known cardiac condition during exercise is rare.[15] However, some lesions are not compatible with competitive sports in view of their physiological complexity and tendency to be associated with serious arrhythmias (Eisenmenger syndrome, PAH, single ventricle palliations with Fontan circulation, unoperated coronary artery anomalies, Ebstein anomaly and ccTGA and TGA repaired by atrial switch or Rastelli procedure among others).[16]

## Pregnancy, Contraception, and Genetic Counseling

The majority of ACHD patients tolerate pregnancy well but are best cared for in a clinical setting with inputs from ACHD cardiology, obstetrics, anesthesia, hematology, neonatology, and genetics. Timely counseling and early involvement of this multidisciplinary team is essential to ensure a successful outcome for the mother and the child. Severe PAH (Eisenmenger patients and others) remains a condition with high maternal (50 percent) and fetal (30–40 percent) mortality; women with this condition should be advised against pregnancy.[17] Other conditions associated with high maternal mortality include severe left outflow/inflow obstructive lesions, poor systemic ventricular function [ejection fraction (EF) <40 percent], and aortic root dilation in Marfan and other related syndromes. Cyanosis poses a significant risk to the fetus, with a live birth unlikely (<12 percent) if oxygen saturation is <85 percent.[18] The significant increase in cardiac output and decrease in peripheral vascular resistance in pregnancy, in conjunction with its hemodynamic consequences for different lesions, must be taken into account and recommendations be made on an individual basis for each lesion. Functional status before pregnancy and history of previous cardiac events are of particular prognostic value. A prospective study identified systemic ventricular EF <40 percent, NYHA class II or more, cyanosis, left heart obstruction (aortic valve area <1.5 $cm^2$ and gradient >30 mm Hg, mitral valve area <2.0 $cm^2$), and prior cardiac events (CHF, stroke, arrhythmia) as risk factors.[19] Patients without these findings and no PAH/mechanical valve or aortic dilation can be considered to be at low risk for a poor outcome from pregnancy.

Fetal echo screening should be recommended at 16 to 18 weeks of gestation. Potential for drugs and their teratogenic effects should be considered, in particular, for patients on warfarin, amiodarone, angiotensin converting enzyme inhibitors, and angiotensin-receptor blockers.

For contraception, barrier methods are safe, protect against sexually transmitted disease, and are effective for compliant couples. Hormonal contraception are efficacious but have limited data regarding safety in ACHD patients and combined oral contraceptives are best avoided in patients with preexisting thrombotic risk (Fontan circulation, cyanotic patients, poor systemic ventricular function). Progesterone-only contraceptives, in contrast to combined pills, have lower thrombotic risk. Progesterone-coated intrauterine devices have high efficacy (>95 percent) and seem to be a reasonable alternative. Sterilization should be considered after careful discussion with family/partner, keeping the long-term prognosis and underlying chromosomal aberrations in mind.

The recurrence rate of CHD in offspring ranges from 2 to 50 percent and risk is higher if mother has CHD than when father is affected. Highest recurrence risks are associated with single gene defects such as Marfan, Noonan, 22q11 deletion syndromes, and Holt Oram syndrome. For others, risk of passing on the defect to the offspring lies between 2 and 4 percent on average and may reach 13 to 18 percent for AS and 6 to 10 percent for ventricular septal defect (VSD).[20]

## Insurance

Despite recommendation from cardiac societies, availability of insurance varies considerably not only between but also within countries, with surprising discordance between insurance policies and available outcome data. Health insurance, in particular, may exclude treatment for the cardiac condition in some countries and has important consequences in "insurance-based medical" systems. Patients currently need to shop around. Problem is more acute for patients with moderate-to-high complexity ACHD and if medical care for these patients is not to be compromised by financial considerations, consistent national strategies for health and life insurance need to be developed.

# SPECIFIC ADULTS WITH CONGENITAL HEART DISEASE LESIONS

Detailed anatomical classification, pathophysiology and its impact on treatment decisions in the pediatric age group is detailed in specific chapters devoted to each lesion in this book. In this section, we will try to highlight issues specific to adults (young and old) with CHD. Some of the general considerations discussed previously apply to all the subsequent sections.

## Atrial Septal Defect

ASD may remain undiagnosed until adulthood as patients are asymptomatic well into their 30s. The majority of these patients will be symptomatic by the fourth decade and present with reduced functional capacity, exertional dyspnea, palpitations and occasionally chest infections/right heart failure. Life expectancy is reduced overall. PAP can be normal but tends to increase with age. Severe PAH, however, is rare (<5 percent) and its development requires additional factors like genetic predisposition (similar to idiopathic PAH). With increasing age and PAP, tachyarrhythmias become more common (atrial flutter/fibrillation-AF)[21] and systemic embolism (paradoxically or from AF) results in premature death and morbidity.

### CLINICAL INVESTIGATION

Key clinical findings include fixed splitting of the second heart sound and a systolic flow murmur over the pulmonary area. Presence of cyanosis in ASD patients should make one suspect: (1) shunt reversal as in Eisenmenger complex; (2) large Eustachian valve directing the inferior vena cava (IVC) flow across the ASD, causing large right-to-left shunt; and (3) Sinus venosus defect of the IVC and superior vena cava (SVC) type, with streaming of desaturated blood to the left atrium. ECG shows incomplete right-heart block with right-axis deviation [superior left-axis deviation in partial atrioventricular septal defect (AVSD)]. Chest x-ray frequently will show increased pulmonary vascularity.

Echocardiography remains the key diagnostic modality to distinguish between the different anatomic ASD variants (secundum, primum, sinus venosus and/or coronary sinus type) as well as relative size, rim, presence of associated mitral valve cleft, drainage of pulmonary veins, and hemodynamic assessment (shunt and PAP). TEE is better at delineating anatomy and should be considered for cases in which device closure is being considered. CMR/CT can help in supplementing echo data, particularly for quantification of RV volume overload and pulmonary venous connections. Cardiac catheterization is required for cases of high PAP to determine PVR and assess operability.

### TREATMENT

Surgical repair has low (<1 percent) mortality and good long-term prognosis, with normal life expectancy when performed at <25 years of age and in absence of PAH.[22] ASD closure after 40 years of age does not affect frequency of arrhythmia development during follow-up but should still be considered as correction improves exercise capacity and stabilizes right heart function,[23] especially if amenable to device closure.

Device closure has become the treatment modality of choice for secundum ASDs with a stretched diameter <38 mm and sufficient rim of 5 mm except toward aorta. This is the case for around 80 percent of secundum ASDs. Atrial tachyarrhythmias after device closure tend to be transient, and complications such as erosion into atrial wall/aorta and thrombo–embolic events are reported in <1 percent cases. Patients require antiaggregant therapy with aspirin for at least 6 months. Studies comparing surgery and catheter-based device closure have reported similar success rates and mortality but with lower morbidity and shorter hospital stay in the nonsurgical cohort.[24]

Poor left ventricular function (systolic and diastolic) may cause pulmonary congestion after ASD closure and may require preinterventional testing with balloon occlusion and hemodynamic assessment. In patients with atrial fibrillation, simultaneous modified Maze procedure should be considered during surgical repair. Closure of ASD should not be considered in patients with Eisenmenger complex. In adults with advanced age and ASDs not amenable to device closure, associated comorbidities should allow individualized recommendations to be made.

### FOLLOW-UP

Patients with prior ASD closure should have assessment of residual shunt, RV size and function, presence of TR and PAP. A history of arrhythmias and an ECG should be obtained and Holter monitoring should be requested accordingly. Patients repaired <25 years of age without any sequelae (no residual shunt, normal PAP/RV and no arrhythmias) do not require regular follow-up and should get in touch with their physicians only if they experience any late-onset arrhythmia. Patients with residual shunt, hemodynamic issues and those repaired >40 years age should be followed regularly in ACHD specialist center.

Late arrhythmias after surgical repair at <40 years of age are mostly intra-atrial reentrant tachycardias/atrial flutter, and are easily amenable to radiofrequency ablation. With or without repair >40 years of age, AF becomes increasingly common and patients should be treated with antiarrhythmics and anticoagulation. Limited data exist on the efficacy of ablation therapy in this subgroup of patients.

### NONCARDIAC CONSIDERATIONS

Asymptomatic ASD patients, pre- or postintervention with normal PAP and no significant history of arrhythmia have no restriction for engaging in sports and exercise. Those with PAH should restrict themselves to low-intensity recreational sports.

The risk from pregnancy in patients without PAH is low. Defect closure prior to conception may reduce the chances of paradoxical embolism and worsening ventricular function during gestation. Pregnancy is contraindicated in patients with Eisenmenger syndrome. Recurrence rate of CHD is 3 to 10 percent (excluding familial ASD and Holt–Oram syndrome with autosomal dominant inheritance).

Prophylaxis for bacterial endocarditis is recommended for 6 months after device or prosthetic patch closure of ASD.

## Ventricular Septal Defect

Excluding bicuspid aortic valve, isolated VSD is the most common congenital malformation at birth (30–40 percent). VSD is also common component of complex anomalies like ToF, ccTGA etc. Spontaneous closure can occur, most often in muscular/trabecular defects, occasionally in perimembranous VSDs, almost never in outlet defects and those that close do it during childhood.

The direction and severity of shunt depends on PVR, size of defect, LV/RV systolic & diastolic function and presence of RVOTO. Clinical presentation in adults could be as: (1) VSD closed in childhood with no residual shunt; (2) closed in childhood but with residual shunt, whose severity and above factors will determine the degree of symptoms; and (3) small VSD with nonprogressive small shunt without LV-volume overload, not considered for repair during childhood. These three categories of patients do not require surgery, especially if they remain asymptomatic.[25]

Patients with large VSD/shunt, LV volume overload and PAH, those with Eisenmenger syndrome and few patients with small defects who will have progressive symptoms need to be assessed and put forward for surgical repair.

Several problems may occur in these patients and each of the issues merits consideration for surgical repair:

- Endocarditis, with a reported incidence of two per 1000 patient years (six times higher than in the normal population)
- Heart failure due to increasing L–R shunt
- Double-chamber right ventricle (DCRV) can develop overtime as a result of the high-velocity VSD jet.
- Discrete sub-AS can develop
- In case of supracristal outlet and high perimembranous defects progressive aortic regurgitation (AR) may develop
- Arrhythmias are less frequent than in other forms of CHD.
- Complete heart block, rare these days, was a common surgical complication requiring permanent pacemakers in older patients. Patients who develop bifascicular or transient trifascicular block after repair are at high risk for developing complete heart block in later years.

### CLINICAL INVESTIGATION

Echocardiography remains the standard investigative modality and provides information on location, number, size of defects, severity of LV volume overload, estimated PAP, and AR due to prolapse of right/noncoronary cusp in case of supracristal and high perimembranous defect. Presence of DCRV must be excluded. CMR is an alternative if echo quality is suboptimal and cardiac catheterization is required only if shunt reversal and established PAH is suspected. It helps to quantify PAP and shunt fraction accurately and can also distinguish between fixed and reversible PAH.

### TREATMENT

Surgical closure with a pericardial patch has low (1-2 percent) operative mortality and with good long-term results, remains the treatment of choice. Transcatheter closure can be considered in patients with increased surgical risk and those that are poorly accessible surgically. Muscular VSDs located centrally in the septum are particularly amenable to treatment with this technique. Long-term data regarding safety and efficacy of catheter-based techniques in all other types of VSD are limited.

### FOLLOW-UP

Patients with LV dysfunction, residual shunt, PAH, AR, RVOTO or left ventricular outflow tract obstruction (LVOTO) should be seen annually. Patients with small isolated VSDs with normal LV/PAP, who are asymptomatic, need to be seen once every 3 to 5 years. After device closure of VSDs, patients should be seen regularly for first 2 years and then the interval can be increased to once every 2 to 5 years.

### NONCARDIAC CONSIDERATIONS

Asymptomatic VSD patients, pre- or postintervention with normal PAP and no significant history of arrhythmia have no restriction for engaging in sports and exercise. Those with PAH should restrict themselves to low-intensity recreational sports.

The risk from pregnancy in patients without PAH is low. Pregnancy is contraindicated in patients with Eisenmenger syndrome. Recurrence rate of CHD is 6 to 10 percent.

Infectious endocarditis prophylaxis is recommended only for those with residual shunts. Patients with patch repair of VSD using prosthetic material should also have IE prophylaxis for the first postoperative 6 months.

## Atrioventricular Septal Defect

AVSDs account for around 3 percent of all CHD. Thirty-five percent of patients with AVSD have Down syndrome. Most complete AVSDs occur in Down patients (>75 percent), and most partial AVSDs occur in non-Down patients (>90 percent). AVSD may occur in association with ToF and other complex heterotaxy syndromes.

Since surgical treatment in the past was frequently withheld for Down syndrome patients, they may frequently present as adults with complete AVSD and Eisenmenger syndrome, unless the VSD is small. Unrepaired partial AVSD is not uncommon in adults. The presenting clinical symptoms are those of L–R shunt and left-AV valve regurgitation in the area of the zone of apposition (also known as "left"). Progressive symptoms develop with increasing age and most patients are symptomatic by 40 years if not operated.

### CLINICAL INVESTIGATION

Clinical presentation mainly depends on the presence and size of ASD/VSD, competence of the AV valves, and direction/degree of shunting. With time, exertional dyspnea, arrhythmia, cyanosis, and sub-AS may progressively develop.

Fifty percent of these patients have prolonged AV conduction and virtually all have left axis deviation. Echocardiography remains the key diagnostic technique and provides assessment of each anatomic component of AV valves and their connections (straddling, overriding), the severity and substrate of AV valve regurgitation, degree and direction of shunting, LV and RV function, PAP, and presence of sub-AS. CMR may be required for accurate quantification of ventricular volume, while cardiac catheterization is indicated in those cases with high PAP where surgical repair is being considered.

### TREATMENT

Repair is surgical as no catheter-based options are available. All symptomatic and asymptomatic patients with echo evidence of moderate-to-severe AV valve regurgitation and impaired LV function should be considered for surgical repair. Surgery should be avoided in patients with Eisenmenger syndrome. Of note, patients with residual shunts requiring pacemakers and high PVR should be considered for epicardial leads in view of increased risk of paradoxical embolism associated with the implantation of intracardiac leads.

### FOLLOW-UP

Lifelong follow-up is recommended for all operated and unoperated patients with AVSD. Particular attention should be paid to residual shunts, AV valve malfunction, LV/RV dysfunction, PAP, sub-AS, and arrhythmias. Patients with no significant defect should be seen every 2 to 3 years and those with residual abnormalities more frequently. One of the most common problems arising during long-term follow-up is increasing left AV valve regurgitation and, in order to preserve the functional integrity of the left ventricle, most patients will require further surgery. This may either be in the form of further repair or replacement of the valve.

### NONCARDIAC CONSIDERATIONS

Asymptomatic AVSD patients (postrepair) have no restriction for engaging in sports and exercise. For residual defects, recommendations should be individualized.

The risk from pregnancy in patients with complete repair and no residual defects is low. AVSD closure prior to conception may reduce the chance of paradoxical embolism and worsening ventricular function. Patients with isolated mild-to-moderate left AV valve regurgitation can tolerate pregnancy well.[26] Pregnancy is contraindicated in patients with Eisenmenger syndrome. Recurrence rate of CHD is high (11 percent), and genetic counseling is necessary. Prophylaxis for IE is recommended for high-risk patients.

## Patent Ductus Arteriosus

Presentations of adult patients with PDA include: (1) asymptomatic patients with small ducts and no signs of LV volume overload; (2) moderate-sized PDA with LV volume overload and occasionally signs of CHF; (3) moderate-sized PDA with predominant PAH and RV dysfunction and finally; and (4) large PDA with Eisenmenger physiology with differential cyanosis (lower extremity and left arm cyanotic as compared to right arm). Risk of endocarditis is small, and rarely aneurysmal duct dilation may compress the left main coronary.

### CLINICAL INVESTIGATION

A continuous machinery murmur, which disappears after development of Eisenmenger syndrome, is typical of this malformation. The role of echo is to look for the presenting features mentioned above and associated complications. CMR and cardiac catheterization are occasionally required.

### TREATMENT

Calcification of the duct is very common in adults and hence device closure (Fig. 90-2) rather than surgical closure is the preferred method, even when other concomitant lesions may necessitate an open repair. Results are good and complication rates of device closure are very low.[27] Surgery is reserved for rare patient with large, aneurysmal duct with unsuitable anatomy. All symptomatic PDAs with signs of LV volume overload should be closed to the exception of patients with Eisenmenger syndrome.

### FOLLOW-UP

Echo evaluations should include LV size and function, PAP, residual shunt, and associated lesions. Patients with no residual shunt, normal LV, and PAP do not require follow-up beyond 6 months. Those with residual shunt, LV dysfunction and PAH should be followed regularly every 1 to 3 years depending on rapidity of deterioration.

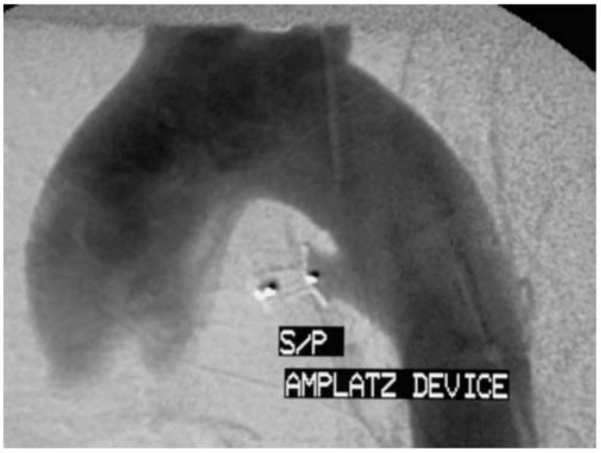



**FIGURE 90-2** Transcatheter closure of patent ductus arteriosus using amplatzer device.

### NONCARDIAC CONSIDERATIONS

Asymptomatic patients, pre- or postintervention with normal PAP have no restriction for engaging in sports and exercise. Those with PAH should restrict themselves to low-intensity recreational sports.

The risk from pregnancy in patients without PAH is low. Pregnancy is contraindicated in patients with Eisenmenger syndrome.

Prophylaxis for IE is recommended for high-risk patients.

## Left Ventricular Outflow Tract Lesions

LVOTO can occur at valvular (most common >75 percent), supra- and subvalvular levels.

## Valvular Aortic Stenosis

Most common cause of valvular AS is congenital bicuspid aortic valve, affecting 1 to 2 percent of the general population. Clinical presentation in adults, management considerations, treatment modalities and follow-up in this group of patients are discussed extensively in the adult cardiac surgery section of this textbook.

## Supravalvular Aortic Stenosis

Supravalvular aortic stenosis (supra-AS) accounts for <7 percent of all forms of fixed LVOTO. It can occur as a localized fibrous diaphragm just distal to coronary ostia or, more commonly, as an external hourglass deformity with corresponding luminal narrowing/diffuse AS. It frequently occurs as a part of the Williams-Beuren syndrome when it is associated with hypoplasia of the entire aorta, involvement of coronary ostia, or stenosis of major aortic branches/PA stenosis. It is important to appreciate that, although site of stenosis may be localized in the ascending aorta, the pathologic process involves the entire aortic root.[28] When present, these lesions are usually significant enough to warrant surgical intervention in infancy/childhood to ensure survival.

Freedom from reoperation at 10 years is 70 to 85 percent with a 10-year actuarial survival of 90 to 95 percent.[29] Reoperation and late death are most commonly related to progressive valve dysfunction and not recurrence of supra-AS.[29] Surgery for diffuse supra-AS as seen with Williams syndrome is less successful, and poor aortic growth persists in both localized and diffuse forms despite successful relief of obstruction initially.[30] These patients are also prone to developing premature CAD.[31]

### TREATMENT

Surgery is the primary treatment. Associated pathologies encountered during follow-up of these patients (AR, recurrent supra-AS, and CAD, which is mostly ostial) needs to be addressed surgically. Indications for surgery include symptomatic patients, asymptomatic patients with Doppler gradient >50 mm Hg, presence of LV dysfunction/severe hypertrophy (LVH, not related to hypertension) and associated CAD. Use of cardiopulmonary exercise testing should be considered when appropriate.

### FOLLOW-UP

Lifelong and regular follow-up including echocardiography is required to determine progression of obstruction/late restenosis, LV size, development of aneurysm and/or pseudoaneurysms postrepair, and presence/progression of CAD.

### NONCARDIAC CONSIDERATIONS

These are similar to valvular AS patients. Genetic evaluation, using fluorescent in situ hybridization, is suggested for family screening in patients with Williams syndrome as their offsprings are at higher risk of recurrence of CHD.

## Subvalvular Aortic Stenosis

Subvalvular AS (Sub-AS) can occur as an isolated lesion, but is frequently associated with a VSD, AVSD, Shone complex or, rarely, may develop after correction of these lesions. The prevalence of 6.5 percent has been reported in the ACHD population and progressive obstruction happens more commonly with increasing age.[32] It is caused by a fibrous ridge/fibromuscular narrowing in the LVOT proximal to the aortic valve and should be distinguished from hypertrophic obstructive cardiomyopathy.

### CLINICAL INVESTIGATION

Clinical findings include ejection systolic murmur at the left sternal border and apex without radiation to the carotid arteries and without any associated ejection clicks. Presence of a diastolic murmur indicates AR.

Echocardiography helps in the initial assessment with visualization of LVOT anatomy, severity of AR, LVH, and LV function. Doppler echocardiography quantifies the severity of subvalvular obstruction but associated LVH and presence of stenotic lesions in series may make the estimate inaccurate. Occasionally, TEE may be required for delineating the membrane.

### TREATMENT

Treatment is indicated in symptomatic patients with mean Doppler gradient of >50 mm Hg and severe AR, in asymptomatic patients with severe AR in presence of LV dysfunction (LVEF <50 percent, LVESD >50 mm), asymptomatic patients with mean Doppler gradient >50 mm Hg, and marked LVH/abnormal blood pressure response on CPET.

Surgical treatment involves circumferential resection of the fibrous ring along with parts of muscular base along the

left septal surface. Diffuse fibromuscular sub-AS requires more extensive root enlargement techniques, such as the modified Konno procedure (Chapter 78). Surgical results are acceptable, but restenosis may occur. In patients with a morphology well-suited for repair and low surgical risk, threshold for intervention should be low, especially since no prosthetic implant is required. In case of moderate-to-severe AR, AVR should be considered at the time of surgery.

### FOLLOW-UP

Lifelong regular follow-up is required to determine progression of obstruction/late restenosis, progression of AR, arrhythmias, heart block, and iatrogenic VSDs.

### NONCARDIAC CONSIDERATIONS

These are similar to valvular AS patients. Pregnancy is contraindicated only in severe symptomatic sub-AS and should be treated to relieve the obstruction before conception.

## Coarctation of Aorta

Coarctation of aorta (CoA) accounts for 5 to 8 percent of all CHD, affecting around 3 per 10,000 live births. Associated lesions include bicuspid aortic valve (up to 85 percent), LVOTO, mitral stenosis (as a part of Shone complex). It is also present in patients with Turner, Willimas–Beuren, congenital rubella syndrome, neurofibromatosis, Takayasu aortitis, and history of trauma.

Key symptoms include headache, epistaxis, dizziness, tinnitus, shortness of breath, abdominal angina, and claudication. The natural course of this malformation may be complicated by the development of left heart failure, intracranial hemorrhage (from Berry aneurysm), IE, aortic rupture/dissection, premature CAD, and stroke.[33]

### CLINICAL INVESTIGATION

Clinical features include upper body systolic hypertension, lower body hypotension and a resulting pressure gradient between the upper and lower halves of the body (>20 mm Hg indicates presence of significant CoA), radio-femoral delay, and palpable collaterals.

Chest x-ray findings may include presence of notched ribs (third–eighth ribs), ectatic ascending aorta, and the "3" sign on chest x-ray secondary to the double contouring of the aorta.

Echocardiography provides information regarding site, structure and extent of CoA, LV function, associated hypertrophy/cardiac anomalies, and aortic and great vessel diameters. Doppler gradients are not useful. Presence of diastolic run-off is a more reliable sign of significance of CoA. In presence of significant collaterals gradients become unreliable and increased systolic flow velocities may develop even in the absence of significant narrowing due to a noncompliant aorta.

CMR/CT are the investigation of choice. Both can evaluate the entire aorta, depict the site and extent of narrowing, and assess the pre- and poststenotic aorta and collaterals. They are extremely useful in detecting complications such as restenosis and aneurysm formation (Fig. 90-1).

Cardiac catheterization with documentation of a peak-to-peak gradient (>20 mm Hg gradient in absence of significant collaterals is significant) still remains the gold standard at many centers for pre- and posttreatment assessment and therapeutic intervention.

### TREATMENT

All symptomatic patients with documented significant gradient across CoA or >50 percent narrowing at the CoA site in comparison with the aortic diameter at the level of diaphragm, presence of upper limb hypertension, significant LVH, and abnormal blood pressure response to exercise are candidates for CoA repair.

Angioplasty and/or stenting has become the treatment of choice in case of native or recurrent/residual CoA in adult patients.[34] The choice between covered or uncovered stents remains controversial. Surgical treatment of coarctation has been extensively covered in Chapter 78.

Repair of recoarctation in adults can be complicated, and ascending-to-descending aortic bypass may be preferable in patients with difficult anatomy. Repair of CoA in older adults carries a significant morbidity, which includes the risk of paraplegia and mortality.[35] Associated lesions such as significant AS/AR, ascending aortic aneurysm, and large Berry aneurysms should be specifically investigated before reintervention for recoarctation is undertaken.

### FOLLOW-UP

Residual sequelae after repair are common and should be screened for during follow-up visits.

- Arterial hypertension at rest or exercise is common even after successful treatment and is an important risk factor for development of premature CAD, CHF, aortic dissection, and stroke.[36]
- Recurrent/residual CoA may exacerbate hypertension and its untoward consequences.
- Aneurysms of ascending aorta/CoA site present a risk of rupture and death.[37] Patch repairs are at particular risk and should be imaged regularly.
- Associated lesions such as bicuspid aortic valve, mitral valve pathologies as a part of Shone complex, premature CAD, and intracranial aneurysm of the circle of Willis should be screened for.

All CoA patients should be followed up at regular intervals with CMR/CT. Frequency of imaging should be based on baseline and postrepair findings.

### NONCARDIAC ISSUES

Patients without residual CoA and with normal blood pressure at rest/exercise can lead a normal life with avoidance of static sports at competition level only. Patients with

hypertension, residual CoA, or other complications should avoid heavy isometric exercises.

Most women after successful treatment of CoA tolerate pregnancy without major problems.[38] Patients with unoperated CoA, postrepair hypertension, residual CoA, or other complications have increased risk of aortic or cerebral aneurysm rupture or dissection during pregnancy/delivery. An excess of miscarriages and hypertensive disorders have been reported in these patients. Prophylaxis for IE is recommended only for high-risk patients.

## Marfan Syndrome

Management of patients with Marfan and other related syndromes have been dealt in detail in the relevant aortic chapters in the adult section of this book as well as in Chapter 82.

## Right Ventricular Outflow Tract Obstruction

RVOTO can occur at the subinfundibular level as seen in DCRV, or at infundibular, valvular, or supravalvular levels; the relevant anatomy, pathophysiological considerations, and syndromic associations of RVOTO have been touched upon within the relevant sections in the congenital cardiac surgery section of this Manual.

Adult patients with unoperated DCRV may be asymptomatic or may present with angina, dyspnea, dizziness, or syncope as the obstruction continues to progress with time.[39] Patients with mild-to-moderate pulmonary valve stenosis (PS) are usually asymptomatic and mild PS in adults usually does not progress.[40] Moderate PS can progress due to valvar calcification reactive myocardial hypertrophy. Once PS is severe almost all patients are symptomatic and have reduced exercise tolerance and, unless operated upon, have poor prognosis. Supravalvar PS is usually seen in syndromic conditions such as Williams, ToF, congenital rubella, etc. and hence should be screened for in the relevant group of patients.

### CLINICAL INVESTIGATION

Clinical findings include a harsh murmur across the obstruction and widely split second heart sound. In peripheral PS the systolic murmur is heard over the lung fields. Findings on CXR may include calcification of pulmonary valve, dilation of main PA, and right heart enlargement.

Echocardiography is essential for anatomic and hemodynamic assessment of lesion severity. It documents the level of RVOTO, pulmonary valve anatomy, and presence of RV hypertrophy (RVH) and coexisting lesions. It provides the gradient across the obstruction, severity of TR/PR (pulmonary regurgitation), and RV pressure overload. Care needs to be taken in distinguishing the jet of DCRV from that of a VSD or infundibular/valvular stenosis. Doppler gradients may overestimate the degree of narrowing in patients with tubular stenosis and in those with stenotic lesions in series. In the patient with DCRV, because of difficulties with axial flow sampling, peak gradients may be underestimated. Use of echo in peripheral PS is less reliable. RVOTO is categorized as mild (peak velocity <3 m/s), moderate (peak velocity 3–4 m/s), and severe (peak velocity >4 m/s). Since Doppler measurements may have an element of uncertainty, accompanying TR velocity assessment with estimation of RV pressure is recommended.[41]

CMR/CT frequently supplement echo assessment and provide additional information in cases with stenosis at subinfundibular/conduit or branch PA levels. CMR is especially suited for evaluating RV function. In conjunction with lung perfusion studies, they are the investigation of choice for peripheral PS. Cardiac catheterization is required only for confirmation of findings of echo/CMR as well as for preoperative coronary angiography.

### TREATMENT

Relief of obstruction with balloon valvotomy is indicated in even in adult patients with severe valvular PS. If unsuitable, surgical valvotomy or rarely surgical valve replacement may be indicated when evidence of progressive RV overload exists (RVSP >80 mm Hg).

Catheter-based intervention is preferable for treating valvular and peripheral PS.[42] Surgery is recommended for patients with DCRV, infundibular PS, hypoplastic pulmonary annulus, and dysplastic pulmonary valve with severe PR/TR. In patients with peripheral PS, surgery may be required in cases of unsuitable anatomy.

The main PA trunk is often markedly dilated in patients with RVOTO; rupture is, however, very rare in this low-pressure system and therefore does not require intervention.[43]

### FOLLOW-UP

Patients with malformations characterized by RVOTO need lifelong annual follow-up with echocardiography except for those with mild PS, who may be seen every 5 years.

### NONCARDIAC ISSUES

Patients with mild PS have no restriction from sports. Those with moderate PS should avoid competitive and static sports, and those with severe PS should restrict themselves to low-intensity recreational sports. Pregnancy is well tolerated except in severe RVOTO with RV failure. Percutaneous valvotomy can be performed during pregnancy is needed. Prophylaxis for IE is recommended only for high-risk groups.

## Ebstein Anomaly

This lesion has also been extensively covered in Chapter 85, and the reader should go back to that section for a detailed description of pathophysiology, anatomical subtypes, techniques of repair, and current surgical results.

### CLINICAL PRESENTATION

Patients not diagnosed until early adulthood may present with a cardiac murmur, cardiomegaly on a chest x-ray, arterial oxygen desaturation, decline in exercise capacity, and/or arrhythmia. Development of atrial flutter or fibrillation may lead to cardiac decompensation in a significant number of patients with this anomaly. The arrhythmia may be caused by progressive tricuspid regurgitation leading to progressive right atrial enlargement. They also may develop Wolff–Parkinson–White syndrome.

### TREATMENT

Medical management of these patients is generally supportive and involves anticoagulation for patients with history of thromboembolism/history of AF. Catheter-based closure of associated ASD/PFO may be considered in acyanotic patients with paradoxical emboli and who are not optimal surgical candidates.

For those patients requiring surgical repair or replacement of the tricuspid valve, cross-sectional echocardiography (both pre- and intraoperatively) has led to a better understanding of valve function. This together with improved surgical techniques has in turn contributed to improved surgical results.

There are several types of surgical repair in the management of Ebstein's anomaly. Tricuspid valve repair and closure of atrial defect is often feasible for symptomatic patients. The atrialized portion of the RV is plicated, the foramen ovale or ASD closed, and either valve repair or replacement is performed. The technique of plication may vary between centers, and would include both a longitudinal and a vertical plication. The technique of valve repair creates essentially a competent monocusp anterior valve leaflet. Closure of the ASD prevents the potential for right-to-left shunting and some may prefer the use of an annuloplasty ring to reinforce the repair. Valve replacement is reserved for significantly dysplastic valves or for reoperative patients. In patients undergoing replacement, a porcine bioprosthesis might lead to improved freedom from structural valve deterioration over bovine pericardial valves.

The Mayo Clinic group reported the surgical results in 189 patients operated between 1972 and 1991. Reoperation was required in 4 patients out of the 110 patients who underwent primary valve repair. This represented 3.6 percent during a follow-up extending to 19 years. In Chavaud's report on 110 patients undergoing surgical intervention for Ebstein malformation only 3 patients underwent valve replacement. Operative mortality was 10 percent in this group. Patients who succumbed in the immediate postoperative period manifested acute right heart failure with severe dysfunction. The addition of a bidirectional superior cavopulmonary shunt was introduced in patients with chronic RV dysfunction to diminish volume load on the RV in the early postoperative phase.

Surgical repair, although challenging, remains the mainstay of treatment. It should be performed only in centers with specific experience with this complex and variable lesion. Tricuspid valve repair or replacement (the latter if repair fails to reduce the residual TR to less than moderate severity) along with closure of ASD is the approach of choice. Tricuspid valve repair by creating a monocusp valve with the mobile anterior leaflet in presence of a functional RV cavity greater than one-third of total RV size has shown good long-term outcomes in experienced hands.[44] Patients with associated tachyarrhythmias should have concomitant surgical flutter ablations or have this addressed in the EP lab. As mentioned above, an additional bidirectional Glenn shunt may be required in cases with small functional RV or preexisting RV dysfunction. In patients with failed repair or severe biventricular failure, heart transplant is an option.

### FOLLOW-UP

Previously reported mortality (>25 percent) has currently fallen to less than 6 percent in specialized centers. Late fatalities are mostly due to arrhythmias. In a large contemporaneous series, survival free of late reoperation was reported at 86, 74, 62, and 46 percent at 5, 10, 15, and 20 years, respectively.[45]

These patients should be followed up annually and be screened for residual/recurrent TR, prosthetic valve complications, RV/LV failure, residual shunts, arrhythmias and high-grade heart block. Recurrent severe TR or failure of the prosthetic valve mandate reintervention.

### NONCARDIAC ISSUES

Patients with no residual anomalies can usually lead normal active lives with the exception of participation in static sports at competitive level. Those with moderate TR, ventricular dysfunction, residual shunts, and arrhythmias should avoid heavy isometric exercises. Women with Ebstein anomaly have carried out successful pregnancies, but those with severe disease are at high risk for both maternal and fetal complications. In some cases, surgical repair should be carried out before a woman becomes pregnant, and careful observation by a specialized obstetric program is indicated following repair and initiation of the gestation.

The spectrum of Ebstein anomaly has perhaps the widest range of presentation of all congenital heart defects, ranging from in-utero demise to the young asymptomatic adult. Adult congenital cardiologists should carefully follow up such patients and be alert for early symptoms of fatigue, cyanosis or rhythm disorders.

Pregnancy is well tolerated in asymptomatic patients with good ventricular function. Those with cyanosis, significant arrhythmias, and right heart failure are significantly increased risk. Risk of CHD to offspring is around 6 percent, and mothers using lithium/benzodiazepines during pregnancy have significantly higher chances of having children with Ebstein anomaly. Prophylaxis for IE is recommended only for high-risk patients.

## Tetralogy of Fallot

ToF is the most common form of cyanotic heart disease after 1 year of age and an overall incidence of 10 percent of all

CHDs. Primary repair between 6 and 18 months is a common practice these days with a perioperative mortality of <1 percent. Late survival after ToF repair is excellent with a 35-year survival around 85 percent.[46]

## Adults without Prior Surgery

In the current era, it is unusual to encounter patients who have not had palliative or corrective surgery for ToF. Many adults with untreated tetralogy may have experienced one or more of the complications associated with cyanosis such as cerebrovascular accident, bacterial endocarditis, paradoxical embolism and brain abscess. Long-term survival without surgery often implies mild pulmonary stenosis during childhood or the development of large-size collateral vessel to augment pulmonary blood flow.

Cardiac catheterization and angiography is indicated to assess RVOTO, the PA anatomy and resistence, as well as the status of the coronary arteries. Patients with favorable anatomy benefit from complete repair, with marked improvement in exercise capacity, elimination of cyanosis, and avoidance of complications associated with right-to-left shunting.

## Adults with Prior Correction of Tetralogy of Fallot

Common complications in adult survivors are:

- Significant PR is present in virtually all patients following transannular patch repair. It is tolerated well hemodynamically for years. Severe chronic PR eventually leads to symptomatic RV dilation and dysfunction.[47] Severity of PR and its deleterious long-term effects on the RV and the tricuspid valve are exacerbated by coexisting PAH and distal PA stenosis.
- Residual RVOTO can occur at any level, from infundibulum to the level of branch PA.
- Tricuspid regurgitation due to RV dilation leads to right atrial enlargement and subsequent development of troublesome atrial tachyarrhythmias.
- Residual VSD due to patch dehiscence or failure of complete closure at the time of surgery leads to progressive LV volume overload.
- Progressive aortic root dilation is seen in 15 percent of adults late after repair and is related to both intrinsic abnormalities of aorta (cystic medial necrosis) and increased flow.[48] It may lead to AR and, very rarely, to true aneurysm formation and aortic dissection or rupture.
- LV dysfunction appearing during follow-up is a risk factor for SCD in ToF patients.[49] It happens due to combination of factors such as inadequate myocardial protection (during operations in the old era), LV volume overload from palliative shunts, and residual VSD and/or AR.
- Tachyarrhythmias are related to progressive hemodynamic sequelae and surgical scarring and are increasingly seen with longer follow-up. SCD is reported in 1 to 6 percent of cases accounting for around a third to half of late deaths.[50]

### CLINICAL INVESTIGATION

Clinical findings in operated patients mostly include a widely split second heart sound, and may include a low-pitched early-ending diastolic murmur of PR, long loud ejection systolic murmur of RVOTO, a high-pitched diastolic murmur of AR, as well as the pansystolic murmur of a residual VSD. ECG shows complete right bundle branch block with wide QRS. A progressively widening QRS >180 ms is risk factor for VT and SCD.[50]

Echocardiography remains the first-line assessment for screening for the above-mentioned issues. CMR has become the method of choice especially for assessment of RV volume and function and provides information about the position of vessels and conduits especially if reoperation is considered. Late enhancement with gadolinium demonstrates extent of fibrosis in the ventricles and has been correlated with the risk of VT and SCD.[51] CT is an alternative to CMR and is especially useful for delineating the extent of conduit calcification, information required for deciding site for percutaneous valve anchorage and for patients with pacemakers and defibrillators in place. Arrhythmias and risk assessment for SCD may need Holter monitoring with event recorder and formal EP testing. Inducible VT in patients with clinical history of arrhythmias and multiple surgeries on RVOT carries a significant risk clinical VT and SCD.[52] Cardiac catheterization is required only for patients undergoing catheter-based interventions (dilation of distal PA stenosis/percutaneous valve implantation) or when noninvasive evaluation is inconclusive.

### TREATMENT

Pulmonary valve replacement and relief of RVOTO can be performed with low mortality (<1 percent) in patients without advanced ventricular dysfunction. Optimal timing of surgery remains a challenge and serial evaluations are more important for making such decisions than isolated measurements. Tissue valves are preferable to mechanical and seem to easily last for 10 to 15 years. Normalization of RV size after reintervention becomes unlikely once the end-diastolic volume index exceeds 160 mL/m$^2$ and recommendation for surgery should be made before reaching this value.[53] Distal PA stenosis, residual VSDs, and AR should also be addressed at the same time. Percutaneous pulmonary valve replacement at present lacks long-term data and is limited by the size range of available prosthesis (16–22 mm only) and the presence of a large outflow tract when a conduit has not been utilized.

EP testing and/or ablation should be performed in patients with symptomatic documented atrial/ventricular arrhythmias. ICD implantation should be considered in appropriate high-risk categories mentioned previously.[50–52] Patients with unexplained syncope should also be formally evaluated and, in absence of reversible cause, undergo placement of an ICD.

### FOLLOW-UP

All patients should have regular follow-up at specialized centers. Frequency of visits and need for echo and/or CMR will be guided by the pathology found and being followed.

### NONCARDIAC ISSUES

There are no restrictions for asymptomatic patients with good hemodynamics. High-risk patients with history of arrhythmias, ventricular dysfunction, and dilated ascending aorta should avoid heavy isometric exercises and only engage in low-intensity sports. Pregnancy is well tolerated in asymptomatic patients with good ventricular function. Those with cyanosis, significant arrhythmias, and right heart failure are at significantly increased risk for maternal and fetal complications. Risk of CHD to offspring is around 3 percent unless the patient has 22q11 deletion when the risk is 50 percent. Prophylaxis for IE is recommended only for high-risk groups.

## Pulmonary Atresia with Ventricular Septal Defect

Pulmonary atresia with VSD (PA-VSD) is at the extreme cyanotic end of the ToF clinical presentation spectrum, and is discussed in detail in Chapter 69.

Late clinical presentation of a repaired PA-VSD patient is similar to that of ToF patients with their associated complications; unrepaired patients will present with exertional dyspnea, fatigue, progressive cyanosis, hemoptysis, CHF, progressive AR and aortic dilation, and arrhythmias.[54]

### CLINICAL INVESTIGATION

Clinical findings may include previously healed thoracotomy or sternotomy scars, cyanosis in unrepaired patients, and continuous murmur in the back, suggesting the presence of multiple aortopulmonary collaterals (MAPCAs). ECG may show right axis deviation and RVH. Chest X-ray will typically disclose a boot-shaped cardiac contour (empty PA bay).

Echocardiography is the first-line investigation and findings will depend on the type of repair. In unrepaired patients, absence of flow from RV to PA and continuous Doppler flow in multiple areas overlying the MAPCAs may be evident. CMR/CT are valuable in the assessment of the lungs and sources of pulmonary blood flow. Cardiac catheterization is, however, mandatory for evaluation of PAH and MAPCAs.

### TREATMENT

Patients surviving to adulthood without repair or those who were palliated[55,56] may benefit from modern surgical and interventional procedures. In particular, patients with good-size confluent PAs, large MAPCAs which are anatomically suited for unifocalization, preserved LV/RV function and absence of severe PAH (due to protecting stenoses) may be considered for repair.[56] All unrepaired patients should be evaluated in centers that specialize in the care of adults with CHD.

By the time of surgical evaluation many patients with severe MAPCAs are not suitable for repair because of complexity of pulmonary vasculature and associated pulmonary hypertension. In rare patients, who are suitable and undergo repair (VSD is closed, RVOTO relief in the setting of normal pulmonary vascular resistance), survival approaches that of ToF patients. Survival, however, falls to 50 to 60 percent at 20 years in patients who are palliated or have incomplete repairs. Heart and lung transplantation outcomes are also worse in this group of patients and, given the paucity of suitable organ donors, they may not have realistic chances of being listed and transplanted.

Catheter-based interventions may include balloon dilation/stenting of collaterals to enhance pulmonary blood flow.[57]

### FOLLOW-UP

These patients should be regularly followed up in specialist ACHD center. Management of cyanosis-related issues and PAH should be carried out according to established guidelines. Patients with changes in their symptoms should be aggressively investigated and treated early.

### NONCARDIAC ISSUES

There are no restrictions for asymptomatic patients with good hemodynamics. High-risk patients with history of arrhythmias and ventricular dysfunction should avoid heavy isometric exercises and only engage in low-intensity sports. Pregnancy is well-tolerated in asymptomatic patients with good ventricular function. Those with cyanosis, significant arrhythmias, and right heart failure are at significantly increased risk of maternal and fetal complications. Risk of CHD in the offspring of patients with 22q11 microdeletion is 50 percent, and screening should be offered to these individuals. Prophylaxis of IE is recommended only for high-risk groups.

## TRANSPOSITION OF THE GREAT ARTERIES

Transposition of the great arteries (TGA) accounts for approximately 5 percent of CHD. It may be an isolated lesion (simple TGA) or associated with other cardiac lesions such as VSD, LVOTO, and CoA (complex transposition). Adult patients present after repair depending on the initial lesion and type of surgical repair.

Most of the present-day adult patients with simple TGA have undergone a Mustard or a Senning atrial switch procedure. Many will have diminished exercise capacity. RV dysfunction (which is the systemic ventricle following these procedures) is a major problem.[58] Tricuspid regurgitation often develops as the RV dilates, and the more severe the systemic dysfunction, the worse the TR. Tachyarrhythmias are also frequent; an atrial flutter, atrial fibrillation and other forms of supraventricular/VT with risk of SCD have been reported.[59] With longer follow-up, worsening sinus node dysfunction requiring permanent pacemaker also becomes common.[60] The atrial baffles can leak (causing either L–R of R–L shunting), or can obstruct (causing either

systemic or pulmonary venous obstruction). The latter (pulmonary venous obstruction) results in PAH. Systemic venous baffle stenosis, mostly superior, is reportedly in up to 25 percent of patients after Mustard repair. This leads to venous congestion of the upper half of body and requires treatment. Similarly, the inferior baffle obstruction causes venous stasis in the lower half of the body and liver congestion. However, systemic venous baffle obstruction can be unnoticed and the patient remains asymptomatic because of presence of decompressing collateral venous drainage in the form of azygos/hemiazygos veins. Narrowing of the subpulmonary outflow tract due to leftward bulging of the interventricular septum can happen but is usually tolerated well by the left ventricle on the right side (subpulmonary) of the circulation.

Young adults who have undergone the arterial switch operation (Chapter 74) largely remain asymptomatic, with majority of them in NYHA functional Class I. Long-term complications include LV dysfunction mainly related to problems with coronary inflow, dilation of ascending aorta with associated AR,[61] supravalvular PS, and PA branch stenosis.

Adult patients with complex transposition who have undergone a Rastelli repair (TGA with PS, in which the anatomical LV is connected through a VSD baffle to the aorta and the RV is connected with a valved conduit to the PA) can be entirely asymptomatic with normal exercise tolerance. Problems encountered during follow-up of these patients are related to conduit stenosis as patients frequently outgrow these residual VSDs and arrhythmias (ventricular/supraventricular).

### CLINICAL INVESTIGATION

Clinical evaluation will involve looking for signs of upper and lower body venous congestion, abnormal murmurs (especially those associated with TR or AR). ECG will frequently show atrial flutter or other arrhythmias. Echo still retains its utility and is very useful in evaluation of ventricular function, TR, baffle leaks, and obstructions including conduit stenosis. TEE is better than TTE (trans-thoracic echocardiogram) in assessing SVC obstruction. CMR/CT supplements echo data on systemic RV function and baffle patency. CPET is very useful in unmasking latent baffle shunts and arrhythmias. Holter monitoring and EP testing are required in high-risk patients. Cardiac catheterization is needed to evaluate PAH and for interventions, coronary flow assessment (radionuclide myocardial perfusion scans may also be used) and when noninvasive investigations are inconclusive.

### TREATMENT

Valve regurgitation in the systemic ventricle should be repaired before the onset of significant dysfunction. Baffle leaks/stenosis (including PA and conduit stenosis) should be treated with catheter-based techniques and, if not successful, then considered for surgical repair. Patients with worsening systemic RV function may be considered for conversion from atrial to arterial switch if the anatomy is suitable[62] or be listed for transplantation. Medical therapy for heart failure with diuretics and digitalis should be commenced as appropriate. The role of ACE inhibitors and β-blockers is less well established in this setting. Coronary malperfusion, AR, and RVOTO gradients >60 mm Hg should be intervened upon in arterial switch patients, based on established guidelines. Percutaneous valve insertion for RV–PA conduit stenosis is an evolving therapeutic modality. Mid-to-long-term data are yet to become available, and this technology cannot be utilized in every patient.[63]

Electrophysiology testing and ablation should be performed by clinicians experienced in treating these conditions because of the complexity of the intra-atrial baffle anatomy. Patients with atrial tachyarrhythmias, impaired RV function, and QRS duration >140 ms are at increased risk of SCD, and should be considered for ICD implant.[64] Epicardial leads should be used whenever feasible.

### FOLLOW-UP

All patients with TGA should be followed up annually in a specialist ACHD center.

### NONCARDIAC ISSUES

Patients with symptoms or history of arrhythmias should be counseled individually. Asymptomatic patients with good hemodynamics should exercise regularly but avoid competitive sports. High-risk patients with history of arrhythmias and ventricular dysfunction should only engage in low-intensity sports. Pregnancy is well tolerated by asymptomatic patients with good ventricular function except by those who have undergone atrial switch procedures who have increased risk of developing serious arrhythmias and irreversible RV dysfunction during pregnancy.[65] Irrespective of the type of repair, TGA patients are at significantly increased risk for premature labor, fetal growth retardation, and miscarriage. Recurrence risk of TGA is low. Prophylaxis of IE is recommended only for high-risk groups.

## Adult Patients with Palliated Univentricular Hearts (Fontan Physiology)

The Fontan operation (Chapter 77) was introduced in 1968, and has become the definitive treatment pathway for a broad range of cardiac malformations characterized by a functionally single ventricle. Currently, total cavopulmonary connection (TCPC) has replaced the atriopulmonary connection (APC) with either an intracardiac or extracardiac conduit between IVC and the PA, together with an SVC–PA anastomosis (bidirectional Glenn). This circulation is established in at least two stages. The operative mortality and subsequent outcome depend on the suitability of the circulation. Strict patient selection (see Chapter 77) gives the best early

and late results with operative mortality of <5 percent in recent series, and includes low PVR and PAP (<15 mm Hg), preserved ventricular function, adequate PA size, absence of significant AV valve regurgitation, and normal regular rhythm.

The lack of a subpulmonary ventricle results in chronic systemic venous hypertension and markedly altered pulmonary hemodynamics. Despite 10 year-survival approaching 90 percent in these patients, it should be appreciated that a premature decline in cardiovascular performance with reduced survival is inevitable even in the best Fontan patient.[66] Hemodynamic derangements contributing to late Fontan failure include a progressive decline in systemic ventricular function, AV valve regurgitation, rise in PVR, atrial enlargement, pulmonary venous obstruction, and consequences of systemic venous hypertension including hepatic congestion.[67] Further complications include atrial and PA thrombus formation, pulmonary arteriovenous malformations, and systemic arterial to pulmonary venous or systemic arterial to PA connection collaterals.

After the Fontan operation, the majority of patients do well during childhood and adolescence albeit with reduced exercise capacity when measured objectively. However, with prolonged (beyond 10 years) follow-up, a notable and progressive decline in exercise performance, development of CHF, cyanosis (especially with a fenestration), and arrhythmias is observed.[68] By 10 years after undergoing the Fontan operation more than 20 percent of patients have supraventricular tachyarrhythmias[69] and it seems that arrhythmias occur less frequent with TCPC than with an APC Fontan.[70]

Protein-losing enteropathy (PLE) is a rare but important complication observed following Fontan palliation, and results in peripheral edema, pleural effusions, and ascites. It can be diagnosed by documenting low serum albumin and elevated α-1-antitrypsin in the stool.[71] It has a very dismal prognosis (5-year survival <50 percent) and available treatments (among which transplantation) are of limited effectiveness.

## CLINICAL INVESTIGATION

Clinical findings include mild nonpulsatile jugular venous distension. Significant jugular venous distension and hepatomegaly should raise the suspicion for Fontan obstruction or ventricular failure. ECG can disclose junctional rhythm or atrial arrhythmias and chest x-ray may show presence of pleural effusion. Annual blood tests should include hematology, serum albumin, and liver and renal function test. When PLE is suspected, α-1-antitrypsin clearance must be calculated. Echo is useful in assessing ventricular and valvular function. For the purpose of imaging the Fontan pathway TEE is somewhat better. CMR/CT can assess the Fontan pathway, collaterals, and pulmonary veins (and rule out right pulmonary venous obstruction by enlarged right atrium or extracardiac Fontan conduit). Liver congestion/cirrhosis (when suspected) is evaluated by ultrasound/CT.

Cardiac catheterization should be performed in cases of unexplained edema, deterioration in exercise capacity, new-onset arrhythmia, worsening cyanosis, and hemoptysis. Catheterization provides information on ventricular and valve function, and hemodynamic measurements including PVR and assessment of obstruction and anomalous vascular connections/collaterals.

## TREATMENT

***Anticoagulation.*** Right atrial blood stasis and disturbed coagulation predispose to thrombosis. The potential for subclinical recurrent pulmonary embolism leading to rise in PVR has led to suggestion by some that lifelong anticoagulation should be considered.[72] However, definitive evidence to support this practice is largely lacking. Anticoagulation is definitely indicated in the presence of atrial thrombus, arrhythmias, or a history of thromboembolic episodes.

***Antiarrhythmic Therapy.*** Loss of sinus rhythm may precipitate rapid hemodynamic decline, and sustained arrhythmia is a true emergency in these patients and should prompt immediate hemodynamic evaluation. Electrical cardioversion is the mainstay of treatment as drug therapy is not as effective and has long-term side effects. There should be a low threshold for radiofrequency ablation in the catheterization laboratory.[73] Antitachycardia atrial pacemakers may help, and if AV pacing is required, epicardial leads should be considered.

***Medical Therapy for PLE.*** Medical therapy remains challenging. After exclusion of hemodynamic problems (Fontan obstruction/occlusion), patients should be put on salt-restricted, high-protein diet, diuretics, ACE inhibitors, steroids, albumin infusion, chronic subcutaneous heparin, and creation of fenestration (by catheter intervention) and eventually, considered for cardiac transplantation.

***Surgical Interventional Options.*** Patients with failing Fontan should be considered for surgery. Conversion of an APC to a more energy efficient TCPC along with arrhythmia ablation at the time of surgery has provided good early results in very experienced hands[74] but has high morbidity and requires permanent pacemaker implantation in majority of cases. Cardiac/heart–lung transplantation remains as options. Significant cyanosis in a fenestrated Fontan or patients with pulmonary arteriovenous malformations may be helped by device closure in the cardiac catheterization laboratory. Fontan pathway obstructions due to clot can also be treated with catheter-directed thrombolysis.

## FOLLOW-UP

Ongoing care of a Fontan patient is highly challenging, and should be performed in an ACHD specialist center annually with echo, ECG, blood tests, and exercise testing. The need for CMR should be based on individual patient status. Comprehensive assessment is mandatory for patients with a

"Failing Fontan" circulation, with particular care to exclude even minor obstruction to cavopulmonary flow and pulmonary venous return.

### NONCARDIAC ISSUES

Patients with Fontan circulation have severely limited exercise capacity and should limit their activities to light recreational sports only. Successful pregnancy is possible in Fontan patients with intensive monitoring during pregnancy and delivery. There is a higher maternal risk if the Fontan circuit is not optimal and higher miscarriage rates if the patient is cyanotic. ACE inhibitors should be withdrawn and anticoagulant management is of course a source of major concern. Prophylaxis for IE is recommended only for high-risk groups including recent redo Fontan (<6 months), cyanosis, prosthetic valve, residual patch leak, and endocarditis.

## Eisenmenger Syndrome and Severe Pulmonary Hypertension

A large proportion of CHD patients (particularly those with relevant systemic-to-pulmonary shunt) will develop PAH if left untreated. Eisenmenger syndrome is seen in CHD with initially large systemic-to-pulmonary shunt, which causes an increase in PVR and ultimately fixed PAH, resulting in shunt reversal and central cyanosis.[75] A recent Dutch registry survey[76] showed the prevalence of PAH (defined by echo RVP measurement) among 1824 ACHD patients with septal defects to be 6.1 percent, with 3.5 percent of patient having Eisenmenger syndrome.

The pathological lesions in ACHD patients with Eisenmenger are very similar to those observed in other forms of PAH.[77] Abnormal vascular shear stress-induced endothelial cell dysfunction plays a major role in its pathogenesis. Initial morphological alterations (medial hypertrophy and intimal proliferation) are potentially reversible; however, with disease progression, advanced changes characterized by plexiform arteriopathy are seen and indicate irreversibility (commonly seen in ACHD).

The current classification[78] of CHD causing PAH takes both clinical and pathological correlates into account and categorizes them into (1) Eisenmenger syndrome (2) moderate-to-large shunt lesions with severe PAH but no shunt reversal/cyanosis yet (3) small defects with PAH (clinical picture similar to idiopathic PAH), and (4) PAH after repair of CHD.

### CLINICAL PRESENTATION

Eisenmenger syndrome is a multiorgan disorder with progressive deterioration. Clinical presentation includes central cyanosis, dyspnea, fatigue, hemoptysis, syncope, and right heart failure in advanced cases. Since patients with reduced arterial oxygen saturation have abnormal hemostasis including thrombocytopenia, they are at risk for both bleeding and thrombosis. In particular, thrombosis of enlarged proximal PA can be found in up to 20 percent of patients and this may cause recurrent pulmonary emboli/infarction and be associated with ventricular dysfunction and reduced pulmonary blood flow.[79]

These patients have reduced survival compared to the age-matched general population[80] although many of them do survive into their 30s and 40s. Survival is, however, better than in patients with idiopathic PAH with comparable functional class. Right heart failure and progressively deteriorating exercise capacity are negative prognostic factors for survival.

### TREATMENT

Use of oral anticoagulation and antiaggregant agents must be individualized to patient-specific risk factors and perceived benefits.

Three classes of drugs, targeted to modifying endothelial cell dysfunction, have recently been approved for treatment of PAH: prostanoids (e.g., epoprostenol), endothelin receptor antagonists (e.g., Bosentan), and phosphodiesterase type-5 inhibitors (e.g., Sildenafil). Their efficacy and safety have been demonstrated in PAH associated with CHD and Eisenmenger syndrome, mostly in the setting of uncontrolled studies. Benefit is mostly in the form of symptom relief and mildly improved exercise capacity but no survival advantage has been shown.

Lung transplantation with repair of cardiac defect or heart–lung transplantation is the final option for these patients especially in those with rapidly declining functional status, and episodes of right-heart failure with elevated levels of B-type natriuretic peptide. Timing of listing remains challenging.

## Management of Cyanotic Patients

Cyanosis is caused by a predominant shunting of deoxygenated blood from the right (pulmonary) to the left (systemic) side. This may occur at the atrial/ventricular level or outside the heart as in pulmonary arteriovenous malformations. Cyanotic patients are broadly categorized within two groups, each with different underlying anatomy and pathophysiology: (1) those with normal or restricted pulmonary blood flow due to an obstruction across RVOTO and (2) those with increased pulmonary blood flow due to the absence of an obstructing lesion and resultant development of PAH and Eisenmenger syndrome. They may have undergone prior palliative procedures.

### ADAPTIVE MECHANISMS

Cyanosis induces adaptive mechanisms to improve oxygen transport and delivery to the tissues. These are secondary erythrocytosis (due to chronic hypoxemia driven erythropoietin secretion), rightward shift of the oxyhemoglobin dissociation curve, and an increase in cardiac output.[81] Compensated erythrocytosis reflects an equilibrium (stable hemoglobin in

an iron-repleted state), and decompensated erythrocytosis indicates failure of an equilibrium (rising hematocrit).

## Multisystem Disorder

Cyanosis and secondary erythrocytosis imply profound consequences on the entire organ system:

- Blood viscosity is increased and is due to increased red cell mass.[82]
- Hemostatic abnormalities are common and attributed to platelet abnormalities (thrombocytopenia and thrombasthenia) and deranged coagulation pathways. Vitamin K-dependent clotting factors (II, VII, IX, and X) and factor V are reduced, fibrinolytic activity is increased, and the levels of von Willebrand factor are low.
- Increased turnover of red blood cells/hemoglobin and impaired uric acid filtration lead to hyperuricemia.[83] The increased concentration of unconjugated bilirubin puts cyanotic patients at risk for calcium bilirubinate stones.
- Severe impairment of endothelium-dependent vasodilation
- Chronic hypoxemia, increased viscosity, and endothelial dysfunction affect microcirculation, myocardial function, and other end-organ function.

### CLINICAL PRESENTATION

Clinical presentation includes central cyanosis, clubbing, and, frequently, scoliosis. Cardiac findings vary depending on the underlying pathophysiology.

These patients have significantly higher mortality compared to their acyanotic ACHD counterparts.[84] Outcome is determined by the underlying anatomy, pathophysiology, palliative procedures, complications of cyanosis, and instituted preventive therapy. Low platelet count, severe hypoxia, cardiomegaly, and elevated hematocrit are useful parameters to predict premature death and adverse events in patients with and without PAH.[85]

### LATE COMPLICATIONS

- Hyperviscosity: symptoms include headache, faintness, dizziness, fatigue, tinnitus, blurred vision, paresthesia in fingers/toes/lips, muscle pain, and weakness. Hyperviscosity symptoms are unlikely in an iron-repleted patient with hematocrit <65 percent.
- Bleeding and thrombotic tendencies cause a therapeutic dilemma. Hemoptysis is the most common major bleeding and is a manifestation of intrapulmonary hemorrhage. Thrombosis occurs due to coagulation abnormalities, blood stasis in dilated chambers and vessels, endothelial dysfunction, presence of thrombogenic prosthetic conduits, and arrhythmias like AF.
- Cerebrovascular accidents may be caused by paradoxical emboli, rheological abnormalities, endothelial dysfunction, and traditional atherosclerotic risk factors. The severity of secondary erythrocytosis was not found to be a risk factor;[86] microcytosis caused by iron deficiency due to inappropriate phlebotomies was the strongest independent predictor of stroke in these patients.[87]
- Paradoxical emboli may be caused by arrhythmias or transvenous leads.
- Iron deficiency is caused by inappropriate phlebotomies.
- Arrhythmias—supraventricular and ventricular.
- Infectious complications include endocarditis, cerebral abscess, and pneumonia.
- Renal dysfunction is common.
- Gall stones.
- Rheumatological complications including gout, hypertrophic osteoarthropathy, and kyphoscoliosis.

### CLINICAL INVESTIGATION

Particular attention must be paid to hyperviscosity symptoms and bleeding/ischemic complications. Oxygen saturation must be obtained with pulse oximetry at rest for at least 5 min and exercise capacity should be assessed on a regular basis, preferably with a 6-min walk test.

Blood work should include tests to screen for all the abovementioned hematological and metabolic derangements.

### TREATMENT

Any proposed intervention should be carefully weighed, and merits particular expertise on the part of the clinician. Acyanotic patients without PAH/Eisenmenger syndrome should be reviewed periodically and, if appropriate, may be considered for Glenn/Fontan-type palliation, while, for those who have not been operated upon, a palliative systemic-to-pulmonary shunt should be considered.

Otherwise, treatment is mostly represented by the medical management of complications.

- Antiarrhythmic therapy should be individualized (medications/ablation/epicardial pacemaker and/or ICD).
- Therapeutic phlebotomy should only be performed in cases with moderate/severe hyperviscosity symptoms (hematocrit >65 percent) and in absence of dehydration and iron-deficiency.
- Blood transfusion may be required in presence of iron repletion.
- Iron supplementation should be performed in presence of iron deficiency (MCV <80 fL) and carefully followed up for rebound effect.
- There are no data to support routine and prolonged therapy with anticoagulants or antiaggregants especially in absence of specific indications such as AF/thromboembolic episodes.
- Hemoptysis requires chest x-ray/CT scan. Bronchoscopy usually is not helpful. Therapy includes general supportive measures and discontinuation of anticoagulation/antiplatelet therapy. Selective embolization of bronchial arteries may be required.
- Asymptomatic hyperuricemia does not need to be treated.

### FOLLOW-UP

All patients require lifelong regular follow-up in a specialist center.

### NONCARDIAC ISSUES

Most patients will only tolerate light recreational sports and should avoid heavy exercise. During daily activities and flights, patients should remain well hydrated. Pregnancy should be avoided because of poor outcomes, and all patients should have prophylaxis for IE.

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## MANAGEMENT OF ADULTS WITH CONGENITAL HEART DISEASE BOARD REVIEW QUESTIONS (CHAPTER 90)

1. Echocardiography is superior to CMR for which of the following conditions?
   A. Quantification of RV volumes and function in ToF
   B. Detection of small mobile vegetations
   C. Evaluation of RVOTO
   D. Assessment of pulmonary insufficiency
   E. Evaluation of collaterals and arteriovenous malformations

2. Which of the following is NOT a cause of cyanosis in an adult patient with isolated ASD?
   A. Eisenmenger syndrome
   B. Sinus venosus ASD, IVC type
   C. Directional flow from a large Eustachian valve
   D. Pulmonary embolism
   E. Sudden left-to-right shunting

3. Which of the following is NOT an indication for intervention in an adult with previous surgical repair of ToF?
   A. Severe pulmonary insufficiency with RV dysfunction
   B. Residual VSD with LV dysfunction
   C. RV outflow tract calcification
   D. Combined aortic dilation and aortic insufficiency
   E. Atrial tachycardia

4. Which of the following is NOT a known long-term complication in an adult patient with prior repair of transposition of the great arteries?
   A. Right atrial tachyarrhythmias
   B. Eisenmenger syndrome
   C. Obstruction to pulmonary venous drainage
   D. Rastelli conduit stenosis
   E. Dilation of the ascending aorta

5. Which of the following is the LEAST common complication encountered during the follow-up of Fontan patients?
   A. Thromboembolism
   B. Arrhythmias
   C. Protein-losing enteropathy
   D. AV valve regurgitation
   E. CHF

## ANSWERS

1. **Answer: B.** CMR is an alternative to echo and is superior in many areas, including quantification of RV volume/ejection fraction in ToF, evaluation of RVOTO, quantification of pulmonary regurgitation, and evaluation of collaterals and arteriovenous malformations. Echocardiography, however, is superior to CMR in estimating gradients, PA pressure and detecting small mobile vegetations.
2. **Answer: E.** Cyanosis occurs in an adult patient with isolated ASD when there is an increase in the amount of desaturated blood reaching the left atrium. Conditions that worsen right-to-left shunting, such as acute PAH from pulmonary embolism or fixed PAH in Eisenmenger syndrome, will cause cyanosis. Streaming of desaturated systemic venous return can also result in cyanosis, such as a large Eustachian valve directing flow from the IVC across the ASD, or IVC-type sinus venosus ASD. Left-to-right shunting does not cause cyanosis.
3. **Answer: C.** Adult patients that have undergone prior repair of ToF may develop a wide range of subsequent conditions and should therefore be monitored for life. Any underlying structural problem that affects cardiac performance, including ventricular dysfunction or arrhythmia, should be promptly addressed. Progressive aortic dilation should also be corrected in order to prevent rupture or dissection. Isolated calcification of a pulmonary homograft used for reconstruction of the RVOT is not an indication for intervention unless there is significant stenosis or insufficiency.
4. **Answer: B.** In general, long-term complications associated with various repairs for transposition of the great arteries are not associated with PAH. Right atrial tachyarrhythmias and obstruction to pulmonary venous drainage are associated with the atrial switch operation. Stenosis of the external pulmonary RV-to-PA conduit can occur after Rastelli-type repair. Dilation of the neoaorta can occur after the arterial switch operation.
5. **Answer: C.** Thromboembolism, arrhythmias, AV valve regurgitation, and CHF are all common complications at long-term follow-up for patients having prior Fontan repair. Protein-losing enteropathy is a relatively rare complication.

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